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The absolute oral bioavailability of selected drugs

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Abstract. Oral bioavailability is best defined as the rate and extent to which an active drug substance is absorbed and becomes available to the general circulation. This concept is discussed, along with several popular methods for determining absolute oral bioavailability. The absolute oral bioavailability of numerous drugs is reviewed and interspecies comparisons are made. In general, absolute oral bioavailability does not correlate well between species, though relative comparisons might be made.

Key words: absolute oral bioavailability – absorption – pharmacokinetics – metabolism

Introduction

The term bioavailability has a variety of definitions and for this reason it is important that it be defined in whatever context it is used. According to Wagner [1979], the FDA originally defined bioavailability as the rate and extent to which an active drug substance is absorbed and becomes available at the site of action. In contrast, realizing the difficulties in measuring drug at the site of action, the American Pharmaceutical Association defines bioavailability as the rate and extent to which an active drug substance is absorbed and becomes available to the general circulation. The latter definition is of more practical use because it permits a fairly simple experimental determination to be made. Recently, the FDA has considered adopting the American Pharmaceutical Association's definition. It is important to note bioavailability is not just a property of the drug itself, but also of the formulation in which the drug is delivered.

Two types of bioavailability will be discussed here. Relative bioavailability is a comparison of the extent and rate of absorption and systemic availability of a drug from two different dose forms and sometimes in comparison to two different routes of administration. Absolute oral bioavailability is a special case in which the extent and rate of absorption and systemic availability of an oral dose is determined relative to an intravenous dose. This review deals strictly with the concept of absolute oral bioavailability and how it is measured.

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A distinction should be made between absorption and bioavailability, because the terms are often incorrectly used interchangeably. For the purpose of this discussion, absorption is defined as the drug passing from the lumen of the gastrointestinal (GI) tract into the tissue of the GI tract. Once into the tissue, the drug is considered absorbed. On the other hand, for a drug to be bioavailable, it must reach the general circulation intact. This is more of a challenge, because once the drug is absorbed it must still pass through the GI tract tissue, the liver, and the lungs before it reaches the general circulation. First-pass metabolism or elimination [Pond and Tozer 1984] in any of these three tissues may destroy or remove a portion of the drug which was absorbed and therefore, reduce the drug's bioavailability. Therefore, on a quantitative basis, the difference between absorption and bioavailability is that amount which is removed or destroyed by first-pass elimination or metabolism. It is possible for a drug to be completely absorbed, yet be entirely destroyed or removed by first-pass metabolism or elimination, so that its absorption is 100% but its oral bioavailability is 0%. Earlier work on this concept was conducted by Harris and Riegelmann [1969] using the metabolism of acetylsalicylate in the dog as a model. The concept is more elegantly presented in the pharmacokinetics handbook by Ritschel [1986].

Methods for determining absolute oral bioavailability of non-prodrugs

By far the most popularly used method for determining absolute oral bioavailability is what will be referred to here as the blood area under the curve (AUC) method. For this method, a drug is administered intravenously and orally and the concentrations of drug in blood (or plasma) are measured at numerous time points.

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The areas under the concentration-time curves are determined (for a discussion of AUC calculation methods, see Ritschel [1984]) and absolute oral bioavailability is calculated according to the following equation:

$$F = \frac{\text{blood AUC}_{po}}{\text{blood AUC}_{iv}} \times \frac{\text{DOSE}_{iv}}{\text{DOSE}_{po}} \qquad \text{(Equation 1)}$$

where F is absolute oral bioavailability and the dose is expressed on a per body wt. basis. The ratio term for the doses allows one to make a linear correction if the oral and intravenous dose levels were different. It is also possible to correct the absolute oral bioavailability for differences in half-life [Gibaldi and Perrier 1982], in which case the equation is:

$$F = \frac{\text{blood AUC}_{po}}{\text{blood AUC}_{iv}} \times \frac{\text{DOSE}_{iv}}{\text{DOSE}_{po}} \times \frac{\text{HL}_{iv}}{\text{HL}_{po}} \qquad \text{(Equation 2)}$$

This correction accounts for differences in the rates of elimination when the drug is administered by the two different routes [Gibaldi and Perrier 1982].

The blood AUC method is generally the method of choice for determinaton of drug availability to the general compartment because it measures drug directly within the systemic circulation. It is most accurate for those drugs which are distributed largely within the central compartment. For drugs with a large volume of distribution, it is less accurate, and should be used with caution.

Another method which is less commonly used is the urine drug excretion method. This method is similar to the blood AUC method, except that the drug concentration is measured in urine instead of blood. This method has the advantage that it is noninvasive. To determine absolute oral bioavailability by the urine drug excretion method, the drug is administered intravenously and orally and urine samples are collected until the drug has been substantially eliminated. Absolute oral bioavailability is then calculated to the equation:

$$F = \frac{\text{urine AUC}_{po}}{\text{urine AUC}_{iv}} \times \frac{\text{DOSE}_{iv}}{\text{DOSE}_{po}} \qquad \text{(Equation 3)}$$

One of the disadvantages of the urine drug excretion method is that its usefulness is limited to those drugs for which significant quantities of intact drug are eliminated in the urine. It should be used with caution for drugs which are eliminated only in small amounts in the urine, due to the inherent error involved in trying to measure small differences between small numbers. Since highly lipophilic drugs in general are not eliminated in the urine due to a high level of plasma protein binding, the urine drug excretion method is generally not useful for highly lipophilic drugs. The blood AUC method should be used instead.

The AUC ratio methods described above may also be applied to other body fluids, such as saliva [Sakai et al. 1983]. As with the urine drug excretion method, this method has the advantage of being noninvasive. However, the use of saliva and other body fluids besides blood is only valid if intact drug is found there in significant amounts.

It is also possible to measure bioavailability of a drug not based on its drug concentrations in blood or urine, but on an observed pharmacological response. This "pharmacodynamic method" may be used if analytical procedures are not available for the drug. It assumes that the active form is the unmetabolized parent drug. The resulting pharmacological availability may differ somewhat from absolute oral bioavailability, due to the fact that there is not always a direct linear relationship between drug concentration and effect. This concept is discussed in more detail by Ritschel [1984 and 1987]. It should be noted that the measurement of bioavailability using a pharmacological response does have the advantage of estimating the availability of the drug to its site of action, according to the FDA's original definition. Therefore, if the goal of an investigation is to measure the effects of different variables on the efficacy of a drug, the use of a pharmacological response may be the method of choice. However, the reader should note that measurements of pharmacological response are often imprecise, and for this reason, pharmacological availability measurements often have a high degree of variability.

In situations where it is not possible to measure intact drug in blood or urine, it is possible to use the concentration of a metabolite to estimate the bioavailability of the parent compound [Wagner 1972]. For this calculation, the assumption is made that metabolism of parent compound to the metabolite is the same for either the intravenous or oral routes of administration. This should be validated prior to using this method, particularly if the drug undergoes first-pass metabolism, because if the metabolite is produced by first-pass metabolism, the absolute oral bioavailability will be overestimated by this method.

It should be emphasized that the methods described above for determining absolute oral bioavailability are really estimates, based on the assumptions that the volumes of distribution, clearance rates, and half-lives for the drug are the same following intravenous and oral administration. These estimates also make the assumptions that the drug does not exhibit saturable metabolism within the range of the doses tested and that the routes of metabolism are constant as the route of administration is varied. If any of these assumptions are not met, then the estimation of absolute oral bioavailability by these methods may be somewhat in error. A number of investigators have proposed models for more accurate determination of absolute oral bioavailability when these assumptions are not met [Rubin and Tozer 1984, Kwan and Till 1973, Collier and Riegelman 1983].

It is often desirable to estimate what the absolute oral bioavailability might be, even though oral dosing data are not available. According to the method of Gibaldi et al. [1971], this can be done if one assumes that absorption is complete and that the loss of drug occurs only due to first-pass metabolism in the liver. It requires an estimate of the blood flow rate to the liver. The equation used is:

$$F = \frac{Q}{Q + D/AUC} \qquad \text{(Equation 4)}$$

where Q is the liver blood flow, D is the dose administered intravenously, and AUC is the area under the intravenous concentration-time curve for intact drug. For drugs which are distributed into the plasma (as opposed to the blood cells), a more accurate estimate may be obtained if plasma concentrations are used to calculate the AUC and Q is expressed as plasma flow rate rather than blood flow rate.

Methods for determining absolute oral bioavailability of prodrugs

Prodrugs [Stella et al. 1985] present a special case for measuring bioavailability because the administered drug is not the active form. It would, therefore, be misleading to calculate the bioavailability according to concentrations of the intact prodrug in blood. It is preferable to measure the concentrations of the active form after administration of the prodrug by the intravenous and oral routes. The oral bioavailability could then be estimated using Equation 1. However, this may lead to an overestimation of bioavailability if all or a portion of the active form is generated by a first-pass mechanism. In this case, one should administer the active drug by the intravenous route and the prodrug by the oral route. The active drug should then be measured in blood or urine, and the oral bioavailability calculated using Equation 1. In this way, the ammount of active drug formed from the orally administered prodrug is compared to an intravenous dose of active drug, which is by definition 100% bioavailable.

Drugs with active metabolites

In cases where the pharmacological activity of a drug is due to multiple circulating active forms, measurement of bioavailability becomes a tricky issue. In some cases, it has been possible to measure the concentrations and relative activities of several contributing metabolites [Marino et al. 1986]. However, this is an arduous task and it involves assumptions which may not be met. In situations such as this, it may be possible to use a single major metabolite to estimate bioavailability. A pharmacological endpoint may also provide a viable alternative for measuring drug bioavailability under these circumstances.

Factors affecting the measurement of absolute oral bioavailability

There are a variety of factors which could affect the assessment of absolute oral bioavailability, and a detailed discussion of each would be beyond the scope of this review. More information on these factors may be found in the reviews by Ritschel [1987a and b], Jollow and Brodie [1972], Pond and Tozer [1984], Melander and McLean [1983] and Bauer et al. [1984]. Several of these factors will, however, be mentioned here as a reminder of the complexity of biological systems.

Obviously, various disease states such as hepatic failure may have major effects on absolute oral bioavailability. This will especially be the case if the drug undergoes first-pass metabolism. For a drug which is administered as the active form, hepatic failure would lead to decreased first-pass metabolism and hence increased bioavailability. However, in the case of a prodrug which is activated by first-pass metabolism, hepatic failure would result in decreased bioavailability.

Strictly speaking, one would not expect renal failure to have a large impact on absolute oral bioavailability, because the effect of renal failure should be similar, regardless of whether the drug was administered orally or intravenously. However, if renal elimination is dose-dependent, renal failure may lead to an apparent change in absolute oral bioavailability if the amount of drug delivered to the systemic circulation following intravenous dosing is different than the amount delivered following oral dosing.

The rate of drug dissolution and drug absorption are important determinants of bioavailability [Jollow and Brodie 1972], particulary for drugs which undergo saturable first-pass metabolism. It follows that characteristics of the gastrointestinal tract such as motility, pH, feeding state and the presence of bile salts would have an effect on drug bioavailability. It would, therefore, be expected that altered GI function may have an impact on bioavailability. This will especially be the case for drugs which undergo first-pass metabolism within the GI tract tissue.

Diurnal variation may have an impact on the measurement of absolute oral bioavailability. It has been reported [Bauer et al. 1984] that such diurnal changes in bioavailability may be due to diurnal changes in drug clearance, among other things.

Absolute oral bioavailability – a review of the published data

For this review, absolute oral bioavailability data on over 400 drugs was collected. The data are shown in Tables 1 and 2. By far, the bulk of the information collected has been obtained in man, but some data are available for experimental animals as well.

The absolute oral bioavailabilities in man range from near zero (buspirone, cephacetrile, cephalothin, cephapirin, cimetropium bromide, coumarin and isoproterenol) to complete (amosulalol, caffeine, cephalexin, diflusinal, ethosuximide, indomethacin, minocycline, pentobarbital, piroxicam, practolol, probenecid and trimethoprim, to name a few). However, most drugs are somewhere in between. Figure 1 shows the frequency distribution of the absolute oral bioavailability of drugs in humans. Surprisingly, the distribution is quite flat, but skewed slightly toward complete bioavailability. It should be noted that this population of data is almost certainly biased, since it represents only those data reported in the literature. There might be numerous drugs whose development was abandoned due to low bioavailability, and for

Table 1. Percent absolute oral bioavailability of drugs. Absolute oral bioavailability has been determined for these drugs by comparison of the plasma or urinary AUCs for intact drug. For the prodrugs which are reported in this table, the bioavailability calculation was done using concentrations of the unconverted prodrug.

Drug	Rodents	Dogs	Primates	Man	References
Acebutolol				37±12	Benet et al. 1984, Meier 1982
Acetaminophen				72±11	Amlie et al. 1979, Clements et al. 1984, Divoll et al. 1982, Forrest et al. 1982
Acetylmethadol	60±8[a]				Henderson et al. 1977
Acetylnormethadol			16±2[b]		Misra et al. 1980
Acetylprocainamide	84–100[a]			92±9	Kamath et al. 1981, Strong et al. 1975, Jacobi et al. 1983
Acetylsalicylate	35[a]	45±8		46–68	Harris and Riegelman 1969, Iwamoto et al. 1982, Needs and Brooks 1985 Pedersen and FitzGerald 1984
Acidocillin				74	Simon et al. 1976
Acyclovir		80–90		15–50	Krasny et al. 1981, Laskin 1983, Peterslund et al. 1984
Alclofenac	88[c]			36–96	Testa et al. 1978, Verbeeck et al. 1983
Alizapride				75–93	Houin et al. 1984
Allopurinol				90±9	Breithaupt and Tittel 1982, Murell and Rapeport 1986
Alprazolam				88	Smith et al. 1984
Alprenolol				9±6	Johnsson and Regardh 1976
Amantadine				95±5	Benet et al. 1984
Amiodarone				22–86	Latini et al. 1984, Pourbaix et al. 1985, Riva et al. 1982
Amitriptyline				46±9	Pond and Tozer 1984, Schulz et al. 1985
Amlodipine				52–88	Faulkner et al. 1986
Amosulalol				100	Nakashima et al. 1984
Amoxicillin				93±10	Arancibia et al. 1980, Spyker et al. 1977
Amphotericin B				<10	Benet et al. 1984
Ampicillin				62±17	Ehrnebo et al. 1979, Tanigawara et al. 1982
Amrinone				93±12	Park et al. 1983
Amsacrine	90±10[c]				Paxton 1986
Aprinidine				85–95	Benet et al. 1984
Atenolol				54±12	Fitzgerald et al. 1978, Johnsson and Regardh 1976, Mason et al. 1979 Meier 1982, Wan et al. 1979
Azosemide				10	Brater et al. 1983
Benzidamine				59–128	Taylor et al. 1987
Benznidazole		130			Workman et al. 1984
Bepridil				60	Benet 1985
Betaxolol				90	Warrington et al. 1980
Biperiden				33±5	Grimaldi et al. 1986
Bretylium				12–37	Garrett et al. 1982, Rapeport 1985
Bromocriptine	6[a]				Schran et al. 1985
Bromopride				49	Brodie et al. 1986
Brotizolam				70±22	Jochemsen et al. 1983 a and b
Budesonide				11±4	Ryerfeldt et al. 1982
Buflomedil				50–80	Clissold et al. 1987
Bufuralol				46±15	Dayer et al. 1982, Tschopp et al. 1978
Bumetanide				66±11	Holazo et al. 1984, Lau et al. 1986
Bupropion				60–80	Benet et al. 1984
Buspirone				3	Gammans et al. 1986
Butylmorphine	10[a]				Butz et al. 1985

Table 1. Percent absolute oral bioavailability of drugs, continued

Drug	Rodents	Dogs	Primates	Man	References
Caffeine				100	Blanchard and Sawers 1983
Canrenoate				100	Beermann and Groschinsky-Grind 1980
Captopril	39–59[a,d]			62	Duchin et al. 1982, Singhvi et al. 1981
Carbamazepine				70	Benet et al. 1984
Carbenicillin				<10	Benet et al. 1984
Carbidopa		88			Obach et al. 1984
CB-1954		40±7			Workman et al. 1986
Cefaclor				90	Benet et al. 1984
Cefadroxil				78–90	Marino et al. 1982
Cefalexin				80–100	Brogard et al. 1978
Cefamandole				96±3	Benet et al. 1984
Cefatrizine				55–77	Pfeffer et al. 1983
Cefoperazone				<10	Benet et al. 1984
Cefoxitin		8±2		78	Benet et al. 1984, Fix et al. 1986
Ceftazidime				<10	Benet et al. 1984
Cefuroxime				1	Foord 1976
Cefuroxime Axetil				23–44	Williams and Harding 1984
Cephacetrile				0	Brogard et al. 1978
Cephalexin				120±16	Schneider et al. 1978
Cephalothin				0	Brogard et al. 1978
Cephapirin				0	Brogard et al. 1978
Cephradine				85±29	Brogard et al. 1978, Philipson et al. 1987, Rattie et al. 1976
Chloprednol				93–99	Mroszcak et al. 1978
Chlorambucil				73–102	Newell et al. 1983
Chloramphenicol				69±13	Ambrose 1984, Kauffman et al. 1981, Kramer et al. 1984, Nahata and Powell 1981
Chloramphenicol Palmitate				80	Ambrose 1984
Chlordiazepoxide				100	Greenblatt et al. 1978
Chlormethiazole				12±3	Blaschke and Rubin 1979, Pentikainen et al. 1978, Pond and Tozer 1984
Chloroquine	69[c]			89–98	Aderounmu et al. 1987, Gustafsson et al. 1983
Chlorothiazide		70+18		33–56	Osman et al. 1982, Resetarits and Bates 1979
Chlorpheniramine	11+8[c]	30–50		25–44	Athanikar and Chiou 1979, Huang et al. 1981 and 1982, Paton and Webster 1985
Chlorpromazine				32±19	Benet et al. 1984
Chlorpropamide				118	Huupponen and Lammintausta 1981
Chlorprothixene				41±21	Roaflaub 1975
Chlortetracycline				25–30	Fabre et al. 1971
Chlorthalidone				64±10	Beermann and Groschinsky-Grind 1980, Fleuren et al. 1979
Cicloprolol				100	Dubruc et al. 1987
Cimetidine				60±10	Arancibia et al. 1985, Bodemar et al. 1981, Okolicsanyi et al. 1982, Richards 1983, Somogyi and Gugler 1983, Somogyi et al. 1980
Cimetropium Bromide				2±1	Imbimbo et al. 1986
Cinromide			35–79[b]		Lane and Levy 1983
Ciprofloxacin				63–77	Hoffken et al. 1985
Cisapride				40–50	Van Peer et al. 1987
Clavulanate				31–99	Bolton et al. 1986, Davies et al. 1985, Nilsson-Ehle et al. 1985

Table 1. Percent absolute oral bioavailability of drugs, continued

Drug	Rodents	Dogs	Primates	Man	References
Clindamycin				85	Benet et al. 1984
Clofibric Acid			74–118[e,f]		Walmsley 1984
Clonazepam		20–60		98±31	Al-Tahan et al. 1984, Benet et al. 1984
Clonidine				87–96	Davies et al. 1977 and 1978
Cloxacillin				37±13	Nauta and Mattie 1976, Spino et al. 1984
Codeine	4[a]			55±5	Butz et al. 1985, Hull at al. 1982, Pond and Tozer 1984
Coumarin	75[a]	45±16	70	3±3	Pond and Tozer 1984, Ritschel et al. 1979
Cyclobenzaprine				52	Hucker et al. 1977
Cyclophosphamide				90–96	Grochow and Colvin 1979, Wagner and Fenneberg 1984
Cyclosporine				20–50	Ptachcinski et al. 1985 and 1986
Dapsone		107±9		93±8	Pieters and Zuidema 1987
Demethylchlor-tetracycline				66	Fabre et al. 1971
Depamide				68±23	Bialer et al. 1987
Desipramine				33–68	Benet et al. 1984
Dexamethasone				53±41	Brophy et al. 1983, Chalk et al. 1984, Eadie et al. 1984, Rose et al. 1981, Workman et al. 1986
Dextromethorphan		12±8			Dixon et al. 1978
Dextropropoxyphene				29–70	Pond and Tozer 1984
Diacetolol				36±5	Flouvat et al. 1981
Diazepam		74–100		98±6	Divoll et al. 1983, Locniskar et al. 1984, Loscher and Frey 1981, Ochs et al. 1982
Diclofenac				58±14	Brune 1985, Willis et al. 1980
Dicloxacillin				49±11	Doluisio et al. 1969, Nauta and Mattie 1976
Diflunisal				100	Verbeeck et al. 1983
Digitoxin				84–93	Vohringer et al. 1977
Digoxin				68±13	Brumbaugh et al. 1983, Doherty et al. 1984, Hager et al. 1981, Pedersen et al. 1983
Dihydrocodeine				12–34	Rowell et al. 1983
Dihydroergosine				10±3	Cvelbar et al. 1987
Dihydroergotamine				52±14	Little et al. 1982
Dihydroergotoxine				5–12	Woodcock et al. 1982
Dilantin				102	Doluisio 1972
Diltiazem		25		24–90	Hermann and Morselli 1985, Hermann et al. 1983, Kohno et al. 1977, Leonard and Talbert 1982, Ochs and Knuchel 1984, Talbert and Bussey 1983
Diphenhydramine				58±12	Blyden et al. 1986, Carruthers et al. 1978, Paton and Webster 1985
Dipyridamole				52±23	Bjornsson and Mahony 1983, Nielsen-Kudsk and Pedersen 1979
Disopyramide		70	5±1[b]	83±11	Bryson et al. 1978, Haskins et al. 1980, Karim et al. 1978, Lima et al. 1984, Siddoway and Woosley 1986
Dixyrazine				10±8	Liedholm et al. 1985
DN-1417 (Peptide)	1[a]	10			Jokohama et al. 1984
Domperidone				14	Heykants et al. 1981
Doxapram				61±19	Robson and Prescott 1978
Doxazosin	50[a]	60		65±14	Kaye et al. 1986, Vincent et al. 1985
Doxepin				13–45	Benet et al. 1984
Doxycycline				93	Fabre et al. 1971
Droloxifene	24–42[a]				Janzen et al. 1987

Table 1. Percent absolute oral bioavailability of drugs, continued

Drug	Rodents	Dogs	Primates	Man	References
Enalapril				43	Dickstein 1986
Encainide				7–82	Gillis and Kates 1984, Pond and Tozer 1984
Endralazine				75	Meredith et al. 1983
Ephedrine	76[d]				Marvola and Kivirinta 1978
Eproxindine				70	Achtert et al. 1987
Ergotamine				2–5	Ibraheem et al. 1983, Perrin 1985
Erythromycin				30–65	Mather et al. 1981
Estradiol Valerate				3±2	Dusterberg et al. 1985
Ethambutol	28[c]			77±8	Benet et al. 1984, Chen et al. 1984
Ethenzamide	18[a]				Shibasaki et al. 1984
Ethimizol				4–22	Trnovec et al. 1985
Ethylmorphine	6[a]				Butz et al. 1985
Ethynylestradiol	15[a]	8±2	64[f]	43±16	Back et al. 1979 and 1981, Hirai et al. 1981, Humpel et al. 1979, Newburger et al. 1983, Orme et al. 1983
Ethosuximide				100±10	Benet et al. 1984
Etilefrine				55	Hengstmann et al. 1975, Pond and Tozer 1984
Etofylline				65–95	Zuidema et al. 1981
Etoposide				17–72	D'Incalci et al. 1982, Stewart et al. 1985
Famotidine				37–45	Campoli-Richards and Clissold 1986
Felodipine	19[a]	17±7		16±6	Baarnhielm et al. 1986, Edgar et al. 1985
Femoxetine				5–10	Lund et al. 1979
Fenflumizole				50	Vinge et al. 1985
Fenfluramine				89±10	Beckett and Brookes 1967
Fenoprofen				80	Rubin et al. 1972
Fenoximone				53	Alken et al. 1984
Flavoxate				90	Bertoli et al. 1976
Flecainide				95	Gillis and Kates 1984
Flucloxacillin				44–54	Benet et al. 1984
Flucytosine				89±10	Gutler et al. 1978, Daneshmend and Warnock 1983
Flunisolide				20±5	Chaplin et al. 1980
Flunitrazepam	69[a]				Becherucci et al. 1985
Fluocortolone				78–89	Tauber et al. 1984
Fluorescein				99	Barry and Behrendt 1985
Fluorouracil				0–74	Cano et al. 1979, Christophidis et al. 1978, Finch et al. 1979, Phillips et al. 1980, Pond and Tozer 1984
Fluoxetine		72			Benfield et al. 1986
Flupentixol				40–55	Jorgensen 1980, Jorgensen et al. 1982
Fosfomycin				37	Cadorniga et al. 1977
Frusemide				63±22	Cutler and Blair 1979
Furosemide	30[a]			63±9	Beermann and Groschinsky-Grind 1980, Grahnen et al. 1984, Lee and Chiou 1983, Ogata et al. 1985, Smith et al. 1980
Gitoxin		91± 8		95	Hupin et al. 1979
Glaziovine		80–98			Marzo et al. 1977
Glipizide				100	Wahlin-Boll et al. 1982
GO-5438		50±18			Hengy et al. 1987
Griseofulvin				95	Benet et al. 1984
Guanabenz			19±3[b]		Meacham et al. 1981
Haloperidol				65±14	Forsman and Ohman 1976, Holley et al. 1983
Hexamethylmelamine	8[a]				Klippert et al. 1983
Hydralazine				26–55	Ludden et al. 1982, Pond and Tozer 1984, Talseth 1976

Table 1. Percent absolute oral bioavailability of drugs, continued

Drug	Rodents	Dogs	Primates	Man	References
Hydrochlorothiazide				72±17	Barbhaiya et al. 1982, Beermann and Groschinsky-Grind 1980
Hydroflumethiazide				50	Beermann and Groschinsky-Grind 1980
Hydromorphone				52	Vallner et al. 1981
Hydroxybutyrate	8[a]				Lettieri and Fung 1976
Hydroxytryptophan				47–84	Magnussen and Nielsen-Kudsk 1980
Ifenprodil	5–9[a]				Durand et al. 1987
Ifosphamide				85–100	McNiel and Morgan 1981
Iloprost				16±4	Krause and Krais 1986
Imipramine				47±21	Abernethy et al. 1984, George 1979, Nagy and Johansson 1975, Pond and Tozer 1984
Indapamide		97			Grebow and Treitman 1981
Indobufen				85	Fucella et al. 1979
Indomethacin	64[a]			85–122	Alvan et al. 1975, Bhat et al. 1980, Brune 1985, Ogiso et al. 1983, Yeh 1985
Interferon			0[g]	5	Benet et al. 1984, Wagner 1972
Isosorbide dinitrate				47–58	Bogaert 1983, Pond and Tozer 1984, Straehl and Galeazzi 1985
Isosorbide-2-mononitrate	100[a]			100	Leitold and Laufen 1983, Straehl and Galeazzi 1985, Straehl et al. 1984
Isosorbide-5-mononitrate				93±18	Major et al. 1984, Steudel et al. 1983, Straehl and Galeazzi 1985, Straehl et al. 1984
Isoproterenol				0	Pond and Tozer 1984
Isotretinoin		21			Cotler et al. 1983
Ketamine				17	Clements et al. 1982
Ketobemidone				34±16	Anderson et al. 1982
Ketoconazole		50±38			Baxter et al. 1986
Ketoprofen	53[a]			85	Julou et al. 1976, Verbeeck et al. 1983
Khellin	6[a]				Said 1982
Labetalol				30±3	Bloschke and Rubin 1979, Daneshmend and Roberts 1982 and 1984, Elliott et al. 1984, Homeida et al. 1978, Louis et al. 1978, Meier 1982
Leucovorin (l)				97±16	Straw et al. 1984
Leucovorin (d)				19±1	Straw et al. 1984
Levodopa		28±3		35	Cotler et al. 1976, Sasahara et al. 1980
Levonorgestrel	67±d[d]			87±9	Back et al. 1981, Gommaa and Osman 1983, Humpel et al. 1978
Lidocaine	8±2[a]	31±13	25±12	34±12	Blaschke and Rubin 1979, Cusack et al. 1985, de Boer et al. 1979, George 1979, Pond and Tozer 1984, Ritschel 1987
Lisuride	28–45[a,c]		5–12[b]	1–50	Humpel et al. 1981 and 1984
Lithium		75±18		95±5	Benet et al. 1984, Ritschel 1987
Lorazepam				64–109	Greenblatt 1981, Greenblatt et al. 1979 and 1982
Lorcainide				35–65	George 1979, Gillis and Kates 1984, Klotz et al. 1978 and 1979, Pond and Tozer 1984
Lormetazepam				70–80	Greenblatt et al. 1983
Maprotiline				36–67	Benet et al. 1984
Mebendazole				22	Dawson et al. 1985
Mecillinam				5	Roholt et al. 1975
Medroxalol				42–82	Elliott et al. 1984
Mefloquine				85	White 1985
Melphalan				72±23	Bosanquet and Gilby 1982, Reece et al. 1986, Woodhouse et al. 1983

Table 1. Percent absolute oral bioavailability of drugs, continued

Drug	Rodents	Dogs	Primates	Man	References
Menogaril	30[d]				McGovren et al. 1984
Mepindolol	1–2[a]	40		82±11	Bonelli et al. 1980, Krause and Kuhne 1983
Meptazinol				2–20	Franklin and Aldrige 1976, Norbury et al. 1983
Mercaptopurine			12±5[b]	16±11	Pond and Tozer 1984, Zimm et al. 1983
Metergoline				23±5	Martini et al. 1983
Metformin				50–60	Pentikainen et al. 1979, Sirtori et al. 1978
Methacycline				58	Fabre et al. 1971
Methadone				79±21	Gourlay et al. 1986, Meresaar et al. 1981, Nilsson et al. 1982a and b
Methimazole				93	Jansson et al. 1985
Methotrexate				36–88	Campell et al. 1985, Christophidis et al. 1979, Harvey et al. 1984
Methotrimeprazine				33–74	Pond and Tozer 1984
Methoxsalen	100[a]	100			Kreuter and Higuchi 1979
Methyldigoxin				41–83	Boerner et al. 1976, Hinderling et al. 1877, Rietbrock et al. 1976
Methyldopa				26±15	Barnett et al. 1977, Dobrinska et al. 1982, Myhre et al. 1982
Methylergometrine				60	Mantyla and Kanto 1981
Methylphenobarbital				73	Hooper et al. 1981
Methylprednisolone				49–81	Antal et al. 1983, Green et al. 1984, Narang et al. 1983
Methyl Proscillaridin				59	Belz et al. 1976
Methysergide				13±4	Bredberg et al. 1986
Metoclopramide	49–91[a]	48		73±25	Bauer et al. 1984, Graffner et al. 1979, Kapil et al. 1984, McGovren et al. 1984, Ross-Lee et al. 1981, Tam et al. 1981, Wright and Pitts 1984
Metopimazine				19±8	Gaillot et al. 1987
Metoprolol				50±11	Hogstedt et al. 1985, Johnsson and Regardh 1976, Johnson et al. 1975, Jordo et al. 1980, Meier 1982, Regardh et al. 1981
Metronidazole		59–100		80–100	Houghton et al. 1979, Mattila et al. 1983, Neff-Davis 1981, Robin et al. 1980, Shaffer et al. 1986, Thiercelin et al. 1984, Urtasun et al. 1983
Mexiletine				78–90	Gillis and Kates 1984, Woosley et al. 1984
Mianserin				20±3	Timmer et al. 1985
Miconazole				25–30	Daneshmend and Warnock 1983
Midalcipran				84±3	Puozzo et al. 1987
Midazolam				33–48	Allonen and Ziegler 1981, Greenblatt et al. 1983, Klotz and Ziegler 1982, Smith et al. 1984
Milrinone				92	Stroshane et al. 1984
Minocycline				100	Benet et al. 1984
Moclobemide				27–70	Raaflaub et al. 1984
Molsidomine				44	Bergstrand et al. 1984
Morphine	31[a]			26±13	Butz et al. 1985, Dahlstrom and Paalzow 1978, Gourlay et al. 1986, Pond and Tozer 1984, Sawe 1986
N-acetylcysteine				9	Olsson et al. 1987
Nadolol				34±5	Meier 1982
Nafcillin				30	Benet et al. 1984
Nafthazone		66			Bressolle and Bres 1985
Nalbuphine	3±1[a]	2–8		7	Aungst et al. 1985, Lo et al. 1984

Table 1. Percent absolute oral bioavailability of drugs, continued

Drug	Rodents	Dogs	Primates	Man	References
Naltrexone				20±5	Bullingham et al. 1983, Wall et al. 1981
Naproxen	50–92[a,h]	68–100		74–97	Frey and Rieh 1981, Lauroba et al. 1986, Runkel et al. 1972 a and b, 1973
Neostigmine				10–20	Aquilonius et al. 1979, Aquilonius and Hartvig 1986, Pond and Tozer 1984
Nicardipine	22–58[a]	9–34	10±3[b]	15–45	Graham et al. 1985, Higuchi and Shiobara 1980, Ling 1984, Sorkin and Clissold 1987
Nifedipine				50±20	Foster et al. 1983, Hermann and Morselli 1985, Kleinbloesem et al. 1985, Leonard and Talbert 1982, Pond and Tozer 1984, Storstein et al. 1984, Talbert and Bussey 1983, Waller et al. 1984
Niguldipine		37			Zech et al. 1987
Nipradilol		11±2			Joshimura et al. 1985
Nitrazepam				78±16	Benet et al. 1984, Jochemsen et al. 1982
Nitrendipine				16±6	Goa and Sorkin 1987
Nitrofurantoin	50[c]	79+11		100	Conklin 1978, Niazi et al. 1983, Watari et al. 1983
Nitroglycerin	2±1[a]				Kamiya et al. 1982
Nomifensine		49		27	Lindberg et al. 1985 and 1986
Norethindrone	53[c]			64±8	Back et al. 1977 and 1978, Orme et al. 1983
Norfenefrin				5	Hengstmann et al. 1975
Norfenfluramine				85±6	Beckett and Brokes 1967
Nortriptyline				50±5	George 1979, Gram and Overo 1975, Pond and Tozer 1984
Norzimelidine				66±18	Brown et al. 1980
Omeprazole				25–100	Clissold and Campoli-Richards 1986, Rohss et al. 1986
Oxazepam		70±15			Alvan et al. 1977
Oxodipine	70[c]	34			Galiano et al. 1987
Oxprenolol				24–60	Johnsson and Regardh 1976, Mason and Winer 1976, Meier 1982, Pond and Tozer 1984
Oxyphenbutazone	104[a]				Lauroba et al. 1986
Oxytetracycline				58	Fabre et al. 1971, von Wittenau 1969
Papaverine		100		23±6	Garrett et al. 1983, Juhran et al. 1975, Pond and Tozer 1984, Ritschel and Hammer 1977
Paracetamol				68–90	Forrest et al. 1982
Pefloxacin				80–110	Barre et al. 1984
Penbutolol				90	Benet et al. 1984
Penicillamine		74±20		41±6	Bergstrom et al. 1981, Kukovetz et al. 1983, Weisner 1981
Penicillin G				15–30	Benet et al. 1984
Penicillin V				60	Benet et al. 1984
Pentacaine	59[a]				Bezek et al. 1986
Pentazocine				18±8	Becket et al. 1970, Pond and Tozer 1984
Pentobarbital	28–76[a]			94±11	Doluisio et al. 1978, Ehrnebo 1974, Knodell et al. 1980, Stella and Chu 1980
Pentoxifylline				19–31	Beerman et al. 1985
Pethidine				48±13	Blaschke and Rubin 1979, Edwards et al. 1982, Herman et al. 1985, Mather and Meffin 1978, Pond and Kretschzmar 1981, Verbeeck et al. 1981
Phenacetin				0–49	Pond and Tozer 1984, Raaflaub and Dubach 1985
Phenazone				81–100	Elfstrom and Lindgren 1978
Phencyclidine				72	Cook et al. 1982
Pheniramine				120	Witte et al. 1985

Table 1. Percent absolute oral bioavailability of drugs, continued

Drug	Rodents	Dogs	Primates	Man	References
Phenobarbital		86–96		96±13	Al-Tahan and Frey 1985, Matsukura et al. 1981, Nelson et al. 1982
Phenylephrine				38	Hengstmann and Goronzy 1982
Phenylethylmalonamide				91±4	Pisani and Richens 1983
Phenytoin		19–68		87±14	Frey and Loscher 1980, Gugler et al. 1976, Hirji et al. 1985, Jusko et al. 1976, Lund et al. 1974, Neuvonen 1979 and 1983
Pholcodine	41[a]				Butz et al. 1985
Physostigmine				0–12	Aquilonius and Hartvig 1986, Whelpton and Hurst 1985
Pimexone				47–84	Grossi et al. 1985
Pinacidil				57±14	McBurney et al. 1985
Pindolol				86±21	Evard et al. 1984, Johnsson and Regardh 1976, Lavene et al. 1977, Meier 1982, Safar et al. 1978
Pipotiazine				26± 8	De Schepper et al. 1979
Pirazolac				88–99	Tauber et al. 1985
Pirmenol				83±24	Gillis and Kates 1984, Lee et al. 1983
Piroxicam	100[a]		84–93[c]	100	Brune 1985, Krause et al. 1983 b, Schiantarelli et al. 1981
Practolol				100	Johnsson and Regardh 1976
Pralidoxime		42–72			Lemanowicz et al. 1979
Prazosin		38±11		57±10	Bateman et al. 1979, Grahnen et al. 1981, Jaillon 1980, Rubin et al. 1979 and 1981, Vincent et al. 1985
Prednisolone		92±17		73–100	Al-Habat and Rogers 1980, Bergrem et al. 1983, Pickup 1979, Tauber et al. 1984, Tse and Welling 1977
Prednisone				100	Uribe et al. 1978
Primaquine	25±26[a]			96± 8	Clark et al. 1984, Mihaly et al. 1985
Primidone				92±18	Benet et al. 1984
Probenecid				100	Cunningham et al. 1981
Probucol	5[a]				Heeg et al. 1984
Procainamide				70±18	Graffner et al. 1975, Manion et al. 1977
Procyclidine				75±15	Whiteman et al. 1985
Progabide			26–45[b]		Johno et al. 1984
Promethazine	25–69[c]			25±10	Paton and Webster 1985, Taylor and Houston 1983, Taylor et al. 1983
Propafenone				5–12	Gillis and Kates 1984
Propiomazine				33	Hartvig et al. 1981
Propoxypenen				100	Selvig 1981
Propoxyphene		28		23–35	George 1979, Olssen et al. 1986
Propranolol (+/−)	10± 3[a]	8–27		2–54	Borgstrom et al. 1981, Heinzow et al. 1984, Hussain et al. 1980, Lo et al. 1982, Tse et al. 1980, Walle et al. 1979, Wilson et al. 1982, Yoshimura et al. 1985
Propranolol (+)		20		19	Walle 1985
Propranolol (−)		19		28	Walle 1985
Propylthiouracil				78±15	Kampmann and Hansen 1981, Kampmann et al. 1979
Proquazone				6–8	Clissold and Beresford 1987
Proscillaridin				7	Pond and Tozer 1984
Protriptyline				77–93	Benet et al. 1984
Proxyphylline				100±7	Selvig 1981
Pyridostigmine				19±15	Aquilonius et al. 1980, Aquilonius and Hartvig 1986

Table 1. Percent absolute oral bioavailability of drugs, continued

Drug	Rodents	Dogs	Primates	Man	References
Pyrimethamine			100		White 1985
Quinidine				44–89	Amlie et al. 1979, Greenblatt et al. 1977, Guentert et al. 1979, Ochs et al. 1980, Rakhit et al. 1984, Ueda et al. 1976, White 1985
Quinine				109	Shann et al. 1985
Ranitidine				53±14	McFadyen et al. 1983, Miller 1984, Morichau-Beachant et al. 1986, Okolicsanyi et al. 1984, Richards 1983, Roberts 1984
Rifampicin				95±17	Loos et al. 1985
Rifampin				50±22	Koup et al. 1986
Saccharin				84±8	Sweatman et al. 1981
Salicylamide	31–44[a,c]				Shibasaki et al. 1981 and 1984
Salicylate	92±2[a]			95±6	Miaskiewicz et al. 1982, Rowland et al. 1972, Yue and Varma 1982
SC-27166	96[a]	27	54–81[f]		Haskins et al. 1978
Sertaconazole	48[a]				Abernethy et al. 1984
SM 1213				63±4	Garrett et al. 1982
Sobrerol (trans)				72±10	Schiavi et al. 1987
Sotalol				60	Johnsson and Regardh 1976, Meier 1982
Sulfadimethoxime		24–86			Baggot et al. 1976, Sams and Baggot 1977
Sulfamethoxazole				100	Benet et al. 1984
Sulfisoxazole				123±11	Kaplan et al. 1972
Sulindac				88	Verbeeck et al. 1983
Sulpiride	4[a]	44–68		27±9	Segura et al. 1976, Wiesel et al. 1980
Suprofen				92	Todd and Heel 1985, Zulliger and Fassolt 1985
Tabernanthine	12[a]				Trouvin et al. 1987
Talindolol				60	Benet et al. 1984
Telenzepine				54	Tschammer et al. 1987
Terazosin				90	Titmarsh and Monk 1987
Terbutaline				22±9	Davis 1984, Hultquist et al. 1984, Nyberg 1984
Terodiline				64–100	Karlen et al. 1982
Testosterone				4±2	Tauber et al. 1986
Tetrabenazine	17[a]			6±3	Mehvar et al. 1987
Tetracycline		10		77–80	Fabre et al. 1971, Raghuram and Krishnaswamy 1981, von Wittenau 1969
Tetrahydrocannabinol				10–20	Wall et al. 1983
Theophylline	39±30[c]	91		65–100[i]	El-Yazigi and Sawchuk 1981, Ingvast-Larsson et al. 1985, Jonkman et al. 1980, Lagas and Jonkman 1985, McKiernan et al. 1981, Tse and Szeto 1982
Tiapamil				22	Wendt 1982
Timolol				30–95	Else et al. 1978, El-Rashidy 1981, Meier 1982, Wilson et al. 1982
Tinidazole				108+47	Bergan 1985, Mattie et al. 1982, Mattila et al. 1983
Tiquizium Bromide		26			Nishikawa et al. 1985
Tocainide				100	Gillis and Kates 1984, Lalka et al. 1976, McDevitt et al. 1976
Tolamolol				30	Johnsson and Regardh 1976, Tschopp et al. 1978
Tolfenamic Acid				56–63	Stenderup et al. 1985, Verbeeck et al. 1983
Toliprolol				90	Benet et al. 1984
Tomoxiprole	50[a]				Assandri et al. 1985
Torasemide				91	Lesne and Clerckx-Braun 1981
Tracazolate		4			Melgar et al. 1984
Tranexamate				34	Pilbrant et al. 1981

Table 1. Percent absolute oral bioavailability of drugs, continued

Drug	Rodents	Dogs	Primates	Man	References
Trazodone	26[a]			85	Benet et al. 1984, Rurak et al. 1981
TRH Tartrate (pep)	1[a]	2–13		2	Yokohama et al. 1984
Triamterene				52±18	Gilfrich et al. 1983, Mutschler et al. 1983
Triflorex	30[a]				Mas-Chamberlin et al. 1981
Trimazosin				61±28	Elliot et al. 1984 b, Reid et al. 1983, Vincent et al. 1985
Trimethadione	94[a]				Tanaka et al. 1981
Trimethoprim				100	Benet et al. 1984
Tulobuterol				48±9	Bres et al. 1987
Valproic Acid				102±25	Bialer et al. 1985, Gugler and von Unruh 1980, Klotz and Antonin 1977, Nitsche and Mascher 1982
Valpromide		65±27			Bialer and Rubinstein 1984
Verapamil (+)				33–65	Vogelgesang et al. 1984
Verapamil (−)				13–34	Vogelgesang et al. 1984
Verapamil (±)		13±3		10–33	Anderson et al. 1982, Arnold et al. 1985, Asthana et al. 1984, Eichelbaum et al. 1981, Leonard and Talbert 1982, McAllister and Kirsten 1982, Talbert and Bussey 1983, Vogelgesang et al. 1984
Viloxazine				85±14	Pisani et al. 1986
Vincamine	58	23–58		20±5	Cadorniga et al. 1984, Ritschel 1987
Warfarin				93±8	Breckenridge and Orme 1973, Holford 1986
Ximoprofen				98	Taylor et al. 1986
Zimelidine				29±14	Brown et al. 1980, Love et al. 1981, Pond and Tozer 1984
Zolpidem	27[a]		1–2[e]	67±4	Thenot et al. 1987, Thiercelin et al. 1987
Zopiclone				80	Goa and Heel 1986

[a]rats, [b]rhesus monkeys, [c]rabbits, [d]mice, [e]cynomolgus monkeys, [f]baboons, [g]african green monkeys, [h]similar results obtained in minipigs, [i]similar results obtained in horses.

Table 2. Percent absolute oral bioavailability of prodrugs. Absolute oral biovailability has been determined for these drugs by comparison of the plasma or urinary AUCs for the active form. Typically, the active form was administered intravenously and the prodrug was administered orally. There are prodrugs which are also reported in Table 1, but those data are derived from concentrations of the unconverted prodrug following oral and intravenous administration.

Prodrug	Active Form	Experimental Animals	Humans	References
Spironolactone	Canrenone	57[a], 48[b]	25±9	Karim et al. 1976, Krause et al. 1983a
Estramustine Phosphate	Estramustine		44±5	Gunnarsson et al. 1984
Azathioprine	6-mercaptopurine	8[b]	60±31	Ding and Benet 1979, Ding et al. 1980
Zimelidine	Norzimelidine		60±6	Brown et al. 1980
Prednisone	Prednisolone		85±19	Rose et al. 1981a and b
Pivaloyloxyethyl Methyldopa	Methyldopa		61±13	Dobrinska et al. 1982
Testosterone Undecanoate	Testosterone		7±3	Tauber et al. 1986
Aminophylline	Theophylline		113	Aslaksen et al. 1981
Enalapril Maleate	Enalaprilat		20	Dickstein 1986
Bacampicillin	Ampicillin		87±22	Bergan 1978
Pivmecillinam	Mecillinam		61	Roholt et al. 1975
Pivamdinocillin	Amdinocillin		44±9	Neu et al. 1983
Acetylmethoxy Cefamandole	Cefamandole	60[c]		Wright et al. 1979
Methylprednisolone Na Succinate	Methylprednisolone		73	Antal et al. 1983

[a]dogs, [b]rhesus monkeys, [c]mice

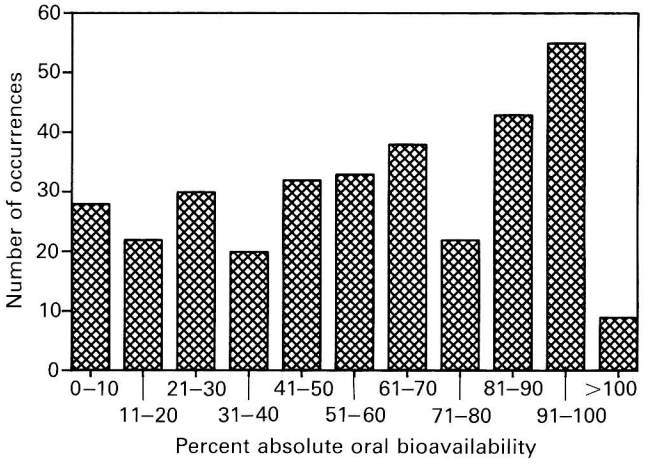


Fig. 1. The absolute oral bioavailability of selected drugs in man. The data shown are derived from Table 1.

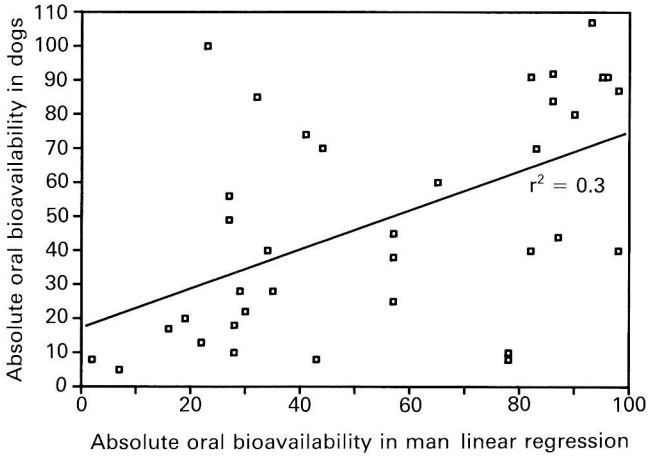


Fig. 3. A comparison of the absolute oral bioavailability of selected drugs in dogs and humans. The data shown are derived from Table 1.

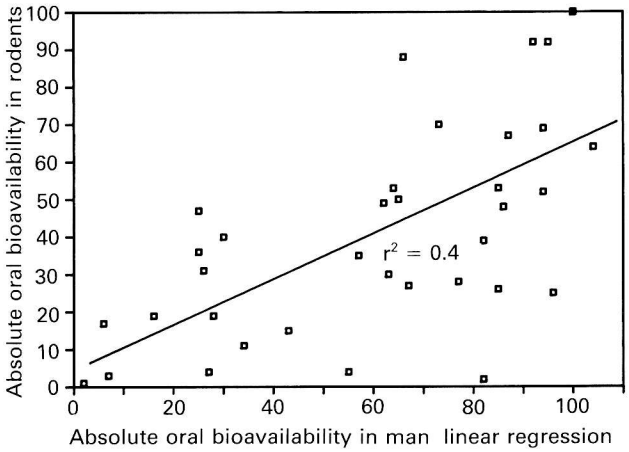


Fig. 2. A comparison of the absolute oral bioavailability of selected drugs in rodents and humans. The data shown are derived from Table 1.

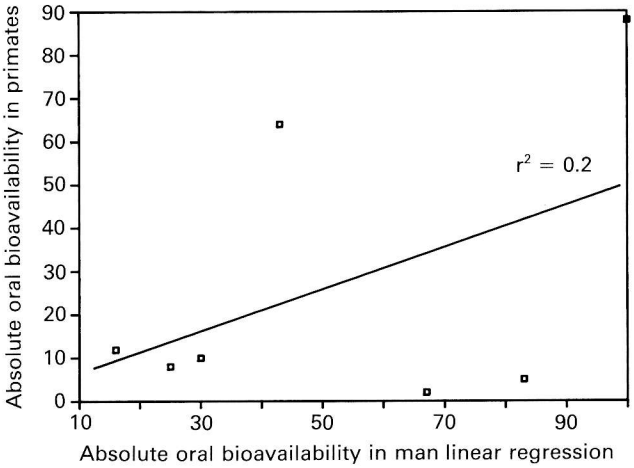


Fig. 4. A comparison of the absolute oral bioavailability of selected drugs in primates and humans. The data shown are derived from Table 1.

which biovailability data have never been published. Therefore, this data set may be under-represented by drugs which have low bioavailability. It is therefore, possible that the true distribution would have an increased frequency of occurrences of low bioavailability.

A number of drugs have highly variable absolute oral bioavailabilities (e. g., acyclovir, alclofenac, amiodarone, benzidamine, desipramine, dexamethasone, dextropropoxyphene, doxepin, encainide, fluorouracil, lisuride, meptazinol, methotrexate, methotrimeprazine, methyldigoxin, moclobemide, omeprazole, phenacetin, propranolol, quinidine, theophylline, and verapamil). Such high variability may be a result of variability in the factors (listed above) which may alter the absolute oral bioavailability of a drug, though the possibility that variability may be due to imprecise clinical or analytical methods should not be discounted. Highly variable bioavailability may affect the efficacy and toxicity of a drug, as discussed below.

For a number of drugs, data are available in both experimental animals and humans. It is interesting to compare the data from various species, though such a comparison suffers from the limitation that the formulations used in animal studies are often different from the formulations used in human studies. The comparisons are shown in Figures 2, 3, and 4 in which the

absolute oral bioavailability in man is plotted against those in rodents, dogs, or primates. Each of the plots is really nothing more than a scatter-gram. A linear regression analysis of the points is indicated on each plot by the line. In each case, there is a very poor correlation between the bioavailability in man and the bioavailability in experimental animals. This is an import observation, because it means that absolute oral bioavailability data in animals may at best be only mildly predictive for what absolute oral bioavailability will be in humans.

Animal species as models for a human absolute oral bioavailability

The finding that animal models are only mildly predictive for humans leads to two very important questions: Why is the absolute oral bioavailability in experimental animals only mildly predictive for humans? And if animals are only mildly predictive for humans, why study absolute oral bioavailability in animals?

In answer to the first question, the lack of predictiveness is most likely related to differences between some of the important variables listed above. In other words, inter-species differences in anatomy and physiology can account for the inter-species variability in absolute oral bioavailability. Such variability is perhaps not so surprising, particulary if one considers that the drugs included in this analysis have a wide range of physical and chemical properties. Inter-species differences in anatomy and physiology (and the effect of these differences on the measurement of bioavailability) are discussed in a more comprehensive fashion in the reviews by Ritschel [1987] and Barr [1972].

In answer to the second question, one should consider very carefully the reason(s) for studying absolute oral bioavailability in experimental animals. If the objective is to predict only what absolute oral bioavailability is in man, then the chances of making an accurate prediction are small. However, if one wants to get a rough picture of how well the drug is absorbed, what factors affect absorption, and whether the drug can undergo first-pass metabolism, then animal experiments will provide useful information. Bioavailability experiments in animals may also help explain results from animal efficacy studies. In many cases, animal experiments may identify a problem with absorption or first-pass metabolism and thereby shift a development team's efforts toward improving absorption, minimizing the effects of first-pass metabolism, or in extreme cases, choosing another drug analog for development.

Impact of low absolute oral bioavailability on the effectiveness of a drug

Low absolute oral bioavailability can result from incomplete absorption or from loss of a drug due to first-pass metabolism. Ordinarily, one would want to maximize bioavailability wherever possible (except in cases where a local action on the GI tract is desired). However, poor oral bioavailability will not compromise the effectiveness of a drug if it is possible to deliver consistent efficacy without increasing the risk of an unacceptable adverse reaction. This concept and the reasoning behind it are discussed in more detail in the paragraphs that follow.

Drugs with low bioavailability often have a large variability in pharmacological response due to an associated variability in drug delivery. This large variability in drug delivery may occur when the bioavailability is low because under those conditions, it takes only a small variation in bioavailability to give a large change in plasma drug concentration. For example, imagine a drug which undergoes a loss of 85% to 95% due to first-pass metabolism and incomplete absorption. The bioavailability of that drug will range from 5 to 15%, and we would expect plasma concentrations to vary as much as 3-fold. Compare that to a drug which undergoes a loss of only 5 to 15%, in which case the corresponding bioavailability would range from 85% to 95%. We would, therefore, expect plasma concentrations to vary only about 12% [(95–85)/85 = 0.12]. Therefore, a potential problem with a drug that has low bioavailability is that it may be difficult to consistently deliver the desired amount of drug.

It would be simple to maintain the efficacy of a poorly bioavailable drug simply by administering an excess of the drug. This is an acceptable therapeutic regimen if there is minimal danger of adverse reactions from a large dose. Penicillin G is an example of a drug which is given in large amounts to make up for its low oral bioavailability. Penicillin G has a very wide therapeutic window and side effects are usually not observed even at very high dose levels.

On the other hand, low bioavailability can represent a real problem for drugs which have a narrow therapeutic window and hazardous adverse reactions. When the therapeutic window is narrow, plasma drug concentrations must be carefully controlled in order to avoid an adverse reaction. The aminoglycoside antibiotics are a good example of this. Their oral bioavailability is poor (less than 5% on average), they have a very narrow therapeutic window, and they could cause very serious adverse reactions. The plasma concentration required for effectiveness is dangerously close to the maximum recommended concentration, above which a potentially lethal nephrotoxicity

can occur. It is not possible to maintain consistent plasma levels of aminoglycosides following oral dosing. Therefore, the aminoglycosides (and other drugs with poor oral bioavailability, narrow therapeutic windows, and hazardous adverse reactions) are generally administered by the intravenous route in order to carefully control plasma drug levels.

The impact, therefore, of low bioavailability on the therapeutic usefulness of a drug depends on whether the drug has a wide or a narrow therapeutic window, and what the seriousness of its adverse reactions are. If the drug can be administered in excess without unacceptable adverse reactions, it could have low absolute oral bioavailability and still be considered safe for oral administration.

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REFERENCES

Abernethy DR, Greenblatt DJ, Shader RI 1984 Imipramine disposition in users of oral contraceptive steroids. Clin Pharmacol Ther *35:* 792–797

Achtert G, Hausleiter HJ, Weimann HJ, Hawkins DR, Darragh A 1987 Pharmacokinetics of the new anti-arrhythmic drug eproxindine HCl after oral administration in phase I. Proc 3rd Eur Congr Biopharm Pharmacokinet Imp Reix Clermont-Ferrand p 344

Aderounmu AF, Lindstrom B, Ekman L 1987 The relationship of the pharmacokinetics of chloroquine to dose in the rabbit. J Pharm Pharmacol *39:* 234–235

Agut J, Saladrich JM, Palacin C, Sacristan A, Oritz JA 1987 Pharmacokinetics of sertaconazole by endovenous, oral, dermal, and vaginal administration to rats. Proc 3rd Eur Congr Biopharm Pharmacokinet Imp Reix Clermont-Ferrand p 213

Alken RG, Belz GG, Heagele KD, Meinicke T, Schechter PJ 1984 Kinetics of fenoximone, a new cardiotonic, in healthy subjects. Clin Pharmacol Ther *36:* 209–216

Allonen H, Ziegler G, Klotz U 1981 Midazolam kinetics. Clin Pharmacol Ther *30 (5):* 653–661

Alvan G, Orme M, Bertilsson L, Ekstrand R, Palmer L 1975 Pharmacokinetics of indomethacin. Clin Pharmacol Ther *18 (3):* 364–373

Alvan G, Jonsson M, Sundwall A, Vessman J 1977 First-pass conjugation and enterohepatic recycling of oxazepam in dogs: Intravenous tolerance of oxazepam in propylene glycol. Acta Pharmacol Toxicol (Suppl) *40 (1):* 16–27

Al-Habat SMH, Rogers HJ 1980 Pharmacokinetics of intravenous and oral prednisolone. Br J Clin Pharmacol *10:* 503–508

Al-Tahan F, Frey HH 1985 Absorption kinetics and bioavailability of phenobarbital after oral administration to dogs. J Vet Pharmacol Ther *8:* 205–207

Al-Tahan F, Loscher W, Frey HH 1984 Pharmacokinetics of clonazepam in the dog. Arch Int Pharmacodyn Ther *268 (2):* 180–193

Ambrose PJ 1984 Clinical pharmacokinetics of chloramphenicol and chloramphenicol succinate. Clin Pharmacokinet *9 (3):* 222–238

Ameer B, Divoll M, Abernethy DR, Greenblatt DJ, Shargel L 1983 Absolute and relative bioavailability of oral acetaminophen preparations. J Pharm Sci *72 (8):* 955–958

Amlie JP, Storstein L, Olsson B, Fremstad D, Jacobsen S 1979 Absolute bioavailability of quinidine in two sustained release preparations. Eur J Clin Pharmacol *16 (1):* 45–48

Anderson P, Arner S, Bondesson U, Boreus LO, Hartvig P 1982a Single-dose kinetics and bioavailability of ketobemidone. Acta Anaesthesiol Scand *(Suppl) 74:* 59–60

Anderson P, Bondesson U, Sylven C 1982 b Clinical pharmacokinetics of verapamil in patients with atrial fibrillation. Eur J Clin Pharmacol *23:* 49–57

Antal EJ, Wright CE, Gillespie WR, Albert KS 1983 Influence of route of administration on the pharmacokinetics of methylprednisolone. J Pharmacokinet Biopharm *11 (6):* 561–576

Aquilonius SM, Hartvig P 1986 Clinical pharmacokinetics of cholinesterase inhibitors. Clin Pharmacokinet *11:* 236–249

Aquilonius SM, Eckernas SA, Hartvig P, Hultman J, Lindstrom B, Osterman PO 1979 A pharmacodynamic study of neostigmine in man using gas chromatography/mass spectrometry. Eur J Clin Pharmacol *15 (5):* 367–371

Aquilonius SM, Eckernas SA, Hartvig P, Lindstrom B, Osterman PO 1980 Pharmacokinetics and oral bioavailability of pyridostigmine in man. Eur J Clin Pharmacol *18 (5):* 423–428

Arancibia A, Guttmann J, Gonzales G, Gonzales C 1980 Absorption and disposition kinetics of amoxicillin in normal human subjects. Antimicrob Agents Chemother *17 (2):* 199–202

Arancibia A, Schindler I, Paccot E, Ruiz I, Gonzales G, Mella F, Thambo S 1985 Pharmacokinetics of cimetidine following administration of a single dose by the rapid intravenous route and by the oral route. Therapie *40 (2):* 87–92

Arnold TH, Tackett RL, Vallner JJ 1985 Pharmacodynamics of acute intranasal administration of verapamil: Comparison with intravenous and oral administration. Biopharm Drug Dispos *6 (4):* 447–454

Aslaksen A, Bakke OM, Vigander T 1981 Comparative pharmacokinetics of theophylline and aminophylline in man. Br J Clin Pharmacol *11 (3):* 269–273

Assandri A, Bernareggi A, Ripamonti A, Perazzi A, Toja E 1985 Pharmacokinetics and metabolism of tomoxiprole, a new analgesic anti-inflammatory agent, in the rat. Eur J Drug Metab Pharmacokinet *10 (2):* 161–170

Asthana OP, Woodcock BG, Wenchel M, Fromming KH, Schwabe L, Rietbrock N 1984 Verapamil disposition and effect on PQ-

intervals after buccal, oral, and intravenous administration. Arzneimittelforschung *34 (4):* 498–502

Athanikar NK, Chiou WL 1979 Chlorpheniramine II. Effect of the first-pass metabolism on the oral bioavailability in dogs. J Pharmaocokinet Biopharm *7:* 383–396

Aungst BJ, Lam G, Shefter E 1985 Oral and rectal nalbuphine bioavailability: First-pass metabolism in rats and dogs. Biopharm Drug Dispos *6:* 413–421

Baarnhielm C, Dahlback H, Skanberg I 1986 In vivo pharmacokinetics of felodipine predicted from in vitro studies in rat, dog, and man. Acta Pharmacol Toxicol *59:* 113–122

Back DJ, Breckenridge AM, Gay FE, Orme MLE, Rowe PH, Smith E 1977 The pharmacokinetics of norethisterone in the rabbit and rat after systemic and oral administration: Effect of phenobarbitone. Br J Pharmacol *60 (2):* 279 P

Back DJ, Breckenridge AM, Crawford FE, MacIver M, Orme MLE, Rowe PH, Smith E 1978 Kinetics of norethindrone in woman II. Single-dose kinetics. Clin Pharmacol Ther *24 (4):* 448–453

Back DJ, Breckenridge AM, Crawford FE, MacIver M, Orme MLE, Rowe PH, Watts MJ 1979 An investigation of the pharmacokinetics of ethynylestradiol in woman using radioimmunoassay. Contraception *20 (3):* 263–273

Back DJ, Bates M, Breckenridge Am, Hall JM, MacIver M, Orme MLE, Park BK, Rowe PH 1981 The pharmacokinetics of levonorgestrel and ethynylestradiol in woman – studies with ovran and ovranette. Contraception *23 (3):* 229–239

Baggot JD, Ludden TM, Powers TE 1976 The bioavailability, disposition kinetics, and dosage of sulphadimethoxime in dogs. Can J Comp Med *40 (3):* 310–317

Barbhaiya RH, Craig WA, Corrick-West HP, Welling PG 1982 Pharmacokinetics of hydrochlorothiazide in fasted and non-fasted subjects: A comparison of plasma level and urinary excretion methods. J Pharm Sci *71 (2):* 245–248

Barnett AJ, Bobik A, Carson V, Korman JS, McLean AJ 1977 Pharmacokinetics of methyldopa. Plasma levels following single intravenous, oral and multiple oral dosage in normotensive and hypertensive subjects. Clin Exp Pharmacol Physiol *4 (4):* 331–339

Barr WH 1972 The use of physical and animal models to assess bioavailability. Pharmacol *8:* 55–101

Barre J, Houin G, Tillement JP 1984 Dose-dependent pharmacodynamic study of pefloxacin, a new antibacterial agent, in humans. J Pharm Sci *73 (10):* 1379–1382

Barry RE, Behrendt WA 1985 Studies on the pharmacokinetics of fluorescein and its dilaurate ester under the conditions of the fluorescein dilaurate test. Arzneimittelforschung *35 (3):* 644–648

Bateman DN, Hobbs DC, Twomey TM, Stevens EA, Rawlins MD 1979 Prazosin, pharmacokinetics and concentration effect. Eur J Clin Pharmacol *16 (3):* 177–181

Bateman DN, Kahn C, Davies DS 1980 The pharmacokinetics of metoclopramide in man with observations in the dog. Br J Clin Pharmacol *9 (4)* 371–377

Bauer LA, Gibaldi M, Vestal RE 1984 Influence of pharmacodynamic diurnal variation on bioavailability estimates. Clin Pharmacokinet *9:* 184–187

Baxter JG, Brass C, Schentag JJ, Slaughter RL 1986 Pharmacokinetics of ketoconazole administered intravenously to dogs and orally as tablet and solution to humans and dogs. J Pharm Sci *75 (5):* 443–447

Becherucci C, Palmi M, Segre G 1985 Pharmacokinetics of flunitrazepam in rats studied by a radioreceptor assay. Pharmacol Res Commun *17 (8):*733–747

Becket AH, Brookes LG 1967 The absorption and urinary excretion in man of fenfluramine and its main metabolite. J Pharm Pharmacol *19 (Suppl):* 41 S – 52 S

Becket AH, Taylor JF, Kourounakis P 1970 The absorption, distribution, and excretion of pentazocine in man after oral and intravenous administration. J Pharm Pharmacol *22 (2):* 123–128

Beermann B, Groschinsky-Grind M 1980 Clinical pharmacokinetics of diuretics. Clin Pharmacokinet *5:* 221–245

Beermann B, Ings R, Mansby J, Chamberlain J, McDonald A 1985 Kinetics of intravenous and oral pentoxifylline in healthy subjects. Clin Pharmacol Ther *37 (1):* 25–28

Belz GG, Schreiter H, Wolf GK 1976 Pharmacokinetics and pharmacodynamics of methyl proscillaridin in healthy man. Eur J Clin Pharmacol *10:* 101–108

Benet LZ 1985 Pharmacokinetics and metabolism of bepridil. Am J Cardiol *55 (7):* 8 C – 13 C

Benet LZ, Massoud N, Gambertoglio JG (eds) 1984 Pharmacodynamic basis for drug treatment. Raven Press, New York

Benfield P, Heel RC, Lewis SP 1986 Fluoxetine. A review of its pharmacokinetic and pharmacodynamic properties, and therapeutic efficacy in depressive illness. Drugs *32:* 481–508

Bergan T 1978 Pharmacodynamic comparison of oral bacampicillin and parenteral ampicillin. Antimicrob Agents Chemother *13 (6):* 971–974

Bergan T 1985 Antibacterial activity and pharmacokinetics of nitroimidazoles. A review. Scand J Infect Dis *46 (Suppl):* 64–71

Bergrem H, Grottum P, Rugstad HE 1983 Pharmacokinetics and protein binding of prednisolone after oral and intravenous administration. Eur J Clin Pharmacol *24:* 415–419

Bergstrand R, Vedin A, Wilhelmsson C, Peterson LE, Chamberlain J, Dell D, Stevens LA, Ostrowski J 1984 Intravenous and oral administration of molsidomine, a pharmacokinetic and pharmacodynamic study. Eur J Clin Pharmacol *27:* 203–208

Bergstrom RF, Kay DR, Wagner JG 1981 The pharmacokinetics of penicillamine in a female mongrel dog. J Pharmacokinet Biopharm *9 (5):* 603–621

Bertoli M, Conti F, Conti M, Cova A, Setnikar I 1976 Pharmacokinetics of flavoxate in man. Pharm Res Commun *8 (4):* 417–428

Bezek S, Scasnar V, Trnovec T, Durisova M, Faberova V, Benes L 1986 The disposition of the local anaesthetic, pentacaine, in rats and mice. Biopharm Drug Dispos *7 (2):* 137–150

Bhat R, Vidyasagar D, Fisher E, Hastreiter A, Ramirez JL, Burns L, Evans M 1980 Pharmacokinetics of oral and intravenous

indomethacin in preterm infants. Dev Pharmacol Ther *1:* 101–110

Bialer M, Rubinstein A 1984 Pharmacokinetics of valpromide in dogs after various modes of administration. Biopharm Drug Dispos *5 (2):* 177–183

Bialer M, Friedman M, Dubrovsky J 1985 Pharmacodynamic evalution of novel sustained-release dosage forms of valproic acid in humans. Biopharm Drug Dispos *6 (4):* 401–411

Bialer M, Friedman M, Rubinstein A, Raz I, Abramsky O 1987 A combined approach to control valproic acid release via a novel delivery system of valpromide. Proc 3rd Eur Congr Biopharm Pharmacokinet Imp Reix Clermont-Ferrand p 110

Bjornsson TD, Mahony C 1983 Clinical pharmacokinetics of dipyridamole. Thromb Res *(Suppl 6):* 93–104

Blanchard J, Sawers SJ 1983 The absolute bioavailability of caffeine in man. Eur J Clin Pharmacol *24 (1):* 93–98

Blaschke TF, Rubin PC 1979 Hepatic first-pass metabolism in liver disease. Clin Pharmacokinet *4:* 423–432

Blyden GT, Greenblatt DJ, Scavone JM, Shader RI 1986 Pharmacokinetics of diphenhydramine and a demethylated metabolite following intravenous and oral administration. J Clin Pharmacol *26 (7):* 529–533

Bodemar G, Norlander B, Walan A 1981 Pharmacokinetics of cimetidine after single doses and during continuous treatment. Clin Pharmacokinet *6: 306–315*

Boerner D, Olcay A, Schaumann W, Weiss W 1976 Absorption of beta-methyl digoxin determined after a single dose and under steady state conditions. Eur J Clin Pharmacol *9 (4):* 307–314

Bogaert MG 1983 Clinical pharmacokinetics of organic nitrates. Clin Pharmacokinet *8:* 410–421

Bolton GC, Allen GD, Davies BE, Filer CW, Jeffery DJ 1986 The disposition of clavulanic acid in man. Xenobiotica *16 (9):* 853–863

Bonelli J, Hitzenberger G, Krause W, Wendt H, Speck U 1980 Pharmacokinetics and pharmacodynamics of mepindolol sulphate. Int J Clin Pharmacol Ther Toxicol *18 (4):* 169–176

Borgstrom L, Johansson C, Larsson H, Leander R 1981 Pharmacokinetics of propranolol. J Pharmacokinet Biopharm *9:* 419–429

Bosanquet AG, Gilby ED 1982 Pharmacokinetics of oral and intravenous melphalan during routine treatment of multiple myeloma. Eur J Cancer Clin Oncol *18 (4):* 355–362

Brater DC, Day B, Anderson S, Seiwell R 1983 Azosemide kinetics and dynamics. Clin Pharmacol Ther *34 (4):* 454

Breckenridge AM, Orme MLE 1973 Kinetics of warfarin absorption in man. Clin Pharmacol Ther *14 (6):* 955–961

Bredberg U, Eyjolfsdottir GS, Paalzow L, Tfelt-Hansen P, Tfelt-Hansen V 1986 Pharmacokinetics of methysergide and its metabolite methylergometrine in man. Eur J Clin Pharmacol *30 (1):* 75–77

Breithaupt H, Tittel M 1982 Kinetics of allopurinol after single intravenous and oral doses: Noninteraction with benzbromarone and hydrochlorothiazide. Eur J Clin Pharmacol *22 (1):* 77–84

Bres J, Clauzel AM, Bressolle F, Visier S, Michel FB 1987 Relationship between plasma concentrations and the effects of tulobuterol on lung function: A kinetic approach. Proc 3rd Eur Congr Biopharm Pharmacokinet Imp Reix Clermont-Ferrand p 373

Bressolle F, Bres J 1985 Pharmacokinetics of naphthazone in the dog. Farmaco [Prat] *40:* 187–198

Brodie RR, Chasseaud LF, Darragh A, Lambe RF, Rooney L, Taylor T 1986 Pharmacokinetics and bioavailability of the antiemetic agent bromopride. Biopharm Drug Dispos 7 (3): 215–222

Brogard JM, Comte F, Pinget M 1978 Pharmacokinetics of cephalosporin antibiotics. Antibiot Chemother *25:* 123–162

Brophy TR, McCafferty J, Tyrer JH, Eadie MJ 1983 Bioavailability of oral dexamethasone during high dose steroid therapy in neurological patients. Eur J Clin Pharmacol *24 (1):* 103

Brown D, Scott DHT, Scott DB, Meyer M, Westerlund D, Lundstrom J 1980 Pharmacokinetics of zimelidine. Systemic availability of zimelidine and norzimelidine in human volunteers. Eur J Clin Pharmacol *17 (2):* 111–116

Brumbaugh GW, Thomas WP, Enos LR, Kaneko JJ 1983 A pharmacodynamic study of digoxin in the horse. J Vet Pharmacol Ther *6 (3):* 163–172

Brune K 1985 Pharmacodynamic factors as causes of variability in response to non-steroidal anti-inflammatory drugs. Agents Actions *17 [Suppl]:* 59–63

Bryson SM, Whiting B, Lawrence JR 1978 Disopyramide serum and pharmacologic effect kinetics applied to the assessment of bioavailability. Br J Clin Pharmacol *6:* 409–419

Bullingham RES, McQuay HJ, Moore RA 1983 Clinical pharmacokinetics of narcotic agonist-antagonist drugs. Clin Pharmacokinet *8:* 332–343

Butz RF, Jones EC, Welch RM, Findlay JWA 1985 Pharmacokinetics and O-dealkylation of morphine-3-alkyl ethers in the rat. A radioimmunoassay study. Drug Metab Dispos *11 (5):* 481–488

Cadorniga R, Diaz Fierros M, Olay T 1977 Pharmacodynamic study of fosfomycin and its bioavailability. Chemotherapy *23 (Suppl 1):* 159–174

Cadorniga R, Saiz Vadillo MC, Molina IT, Cadorniga L 1984 Pharmacodynamic study of vincamine teprosilate. Int J Clin Pharmacol Res *4 (4):* 281–290

Campbell MA, Perrier DG, Dorr RT, Alberts DS, Finley PR 1985 Methotrexate: bioavailability and pharmacokinetics. Cancer Treat Rep *69 (7):* 833–838

Campoli-Richards DM, Clissold SP 1986 Famotidine. Pharmacokinetic and pharmacodynamic properties and a preliminary review of its therapeutic use in peptic ulcer disease and Zollinger-Ellision syndrome. Drugs *32:* 197–221

Cano JP, Rigault JP, Aubert C, Carcassonne Y, Seitz JF 1979 Determination of 5-fluorouracil in plasma by GC/MS using an internal standard. Applications to pharmacokinetics. Bull Cancer *66 (1):* 672–74

Carruthers SG, Schoeman DW, Hignite CE, Azarnoff DL 1978 Correlation between plasma diphenhydramine level and sedative and antihistamine effects. Clin Pharmacol Ther *23 (4):* 375–382

Chalk JB, Ridgeway K, Brophy T, Yelland JD, Eadie MJ 1984 Phenytoin impairs the bioavailability of dexamethasone in neurological and neurosurgical patients. J Neurol Neurosurg Psychiatry *47 (10):* 1087–1090

Chaplin MD, Brooks W, Swenson EW, Cooper WC, Nerenberg C, Chu NI 1980 Flunisolide metabolism and dynamics of a metabolite. Clin Pharmacol Ther *27 (3):* 402–413

Chen MM, Lee CS, Perrin JH 1984 Absorption and disposition of ethambutol in rabbits. J Pharm Sci *73 (8):* 1053–1055

Christophidis N, Vajda FJ, Lucas I, Drummer O, Moon WJ, Louis WJ 1978 Fluorouracil therapy in patients with carcinoma of the large bowel. Clin Pharmacokinet *3 (4):* 330–336

Christophidis N, Vajda FJ, Lucas I, Moon WJ, Louis WJ 1979 Comparison of intravenous and oral high-dose methotrexate in treatment of solid tumors. Br Med J *1 (6159):* 298–300

Clark AM, Baker JK, McChesney JD 1984 Excretion, distribution, and metabolism of primaquine in rats. J Pharm Sci *73 (4):* 502–506

Clements JA, Nimmo WS, Grant IS 1982 Bioavailability, pharmacokinetics, and analgesic activity of ketamine in humans. J Pharm Sci *71 (5):* 539–542

Clements JA, Critchley JAJH, Prescott LF 1984 The role of sulphate conjugation in the metabolism and disposition of oral and intravenous paracetamol in man. Br J Clin Pharmacol 18: 481–485

Clissold SP, Campoli-Richards DM 1986 Omeprazole. A preliminary review of its pharmacokinetic and pharmacodynamic properties, and therapeutic potential in peptic ulcer disease and Zollinger-Ellison syndrome. Drugs *32 (1):* 15–47

Clissold SP, Beresford R 1987 Proquazone. A review of its pharmacokinetic and pharmacodynamic properties, and therapeutic efficacy in rheumatic diseases and pain states. Drugs *33 (5):* 478–502

Clissold SP, Lynch S, Sorkin EM 1987 Buflomedil. A review of its pharmacokinetic and pharmacodynamic properties, and therapeutic efficacy in peripheral and cerebral vascular diseases. Drugs *33 (5):* 430–460

Collier PS, Riegelman S 1983 Estimation of absolute bioavailability assuming steady state apparent volume of distribution remains constant. J Pharmacokinet Biopharm *11 (2):* 205–214

Conklin JD 1978 The pharmacokinetics of nitrofurantoin and its related bioavailability. Antibiot Chemother *25:* 233–252

Connolly SJ, Kates RE 1982 Clinical pharmacokinetics of N-acetylprocainamide. Clin Pharmacokinet *7:* 206–220

Cook CE, Brine DR, Jeffcoat AR, Hill JM, Wall NE, Perez-Reyes M, Di Guiseppi SR 1982 Phencyclidine disposition after intravenous and oral doses. Clin Pharamcol Ther *31 (5):* 625–634

Cotler S, Holazo A, Boxenbaum HG, Kaplan SA 1976 Influence of route of administration on physiological availability of levodopa in dogs. J Pharm Sci *65 (6):* 822–827

Cotler S, Bugge CJ, Colburn WA 1983 Role of gut contents, intestinal wall, and liver on the first-pass metabolism and absolute bioavailability of isotretinoin in the dog. Drug Metab Dispos *11 (5):* 458–462

Cunningham RF, Israili ZH, Dayton PG Clinical pharmacokinetics of probenecid. Clin Pharmacokinet *6:* 135–151

Cusack B, O'Malley K, Lavan J, Noel J, Kelly JG 1985 Protein binding and disposition of lignocaine in the elderly. Eur J Clin Pharmacol *29:* 323–329

Cutler RE, Blair AD 1979 Clinical pharmacokinetics of frusemide. Clin Pharmacokinet *4:* 279–296

Cutler RE, Blair AD, Kelly MR 1978 Flucytosine kinetics in subjects with normal and impaired renal function. Clin Pharmacol Ther *24 (3):* 333–342

Cvelbar P, Kopitar Z, Culig J, Lenardic A, Urbancic-Smerkolj J, Zorz M 1987 Bioavailability of dihydroergosine in healthy volunteers. Proc 3rd Eur Congr Biopharm Pharmacokinet Imp Reix Clermont-Ferrand p 310

Dahlstrom BE, Paalzow LK 1978 Pharmacodynamic interpretation of the enterohepatic recirculation and first-pass elimination of morphine in the rat. J Pharmacokinet Biopharm *6 (6):* 505–519

Daneshmend TK, Roberts CJC 1982 The influence of food on the oral and intravenous pharmacokinetics of a high clearance drug: A study with labetalol. Br J Clin Pharmacol *14:* 73–78

Daneshmend TK, Warnock DW 1983 Clinical pharmacokinetics of systemic antifungal drugs. Clin Pharmacokinet *8:* 17–42

Daneshmend TK, Roberts CJC 1984 The effects of enzyme induction and enzyme inhibition on labetalol pharmacokinetics. Br J Clin Pharmacol *18:* 393–400

Davies BE, Coates PE, Clarke JGN, Thawley AR, Sutton JA 1985 Bioavailability and pharmacokinetics of clavulanic acid in healthy subjects. Int J Clin Pharmacol Ther Toxicol *23:* 70–73

Davies DS 1984 Pharmacokinetics of terbutaline after oral administration. Eur J Resp Dis *65 (Suppl 134):* 111–117

Davies DS, Wing LMH, Reid JL, Neill E, Tippett P, Dollery CT 1977 Pharmacokinetics and concentration-effect relationships of intravenous and oral clonidine. Clin Pharmacol Ther *21 (5):* 593–601

Davies DS, Neil E, Reid JL 1978 Applications of deuterium labelling in pharmacodynamic and concentration-effect studies of clonidine. In: *Baille TA (ed),* Stable Isotopes, University Park Press pp 45–51

Dawson M, Braithwaite PA, Roberts MS, Watson TR 1985 The pharmacokinetics and bioavailability of a tracer dose of [^{3}H]-mebendazole in man. Br J Clin Pharmacol *19 (1):* 79–86

Dayer P, Balant L, Courvoisier F, Kupfer A, Kulbi A, Gorgia A, Fabre J 1982 The genetic control of bufuralol metabolism in man. Eur J Drug Metab Pharmacokinet *7 (1):* 73–77

de Boer AG, Breimer DD, Mattie M, Pronk J, Gubbens-Stibbe JM 1979 Rectal bioavailability of lidocaine in man: Partial avoidance of first-pass metabolism. Clin Pharmacol Ther *26 (6):* 701–709

De Schepper PJ, Vranckx C, Verbeeck R, Van den Berghe MLO 1979 Pipotiazine pharmacokinetics after p.o. and i.v. administration in man. Arzneimittelforschung *29:* 1056–1066

Dickstein K 1986 Pharmacokinetics of enalapril in congestive heart failure. Drugs *32 (Suppl 5):* 40–44

Ding TL, Benet LZ 1979 Comparative bioavailability and pharmacodynamic studies of azathioprine and 6-mercaptopurine in the rhesus monkey. Drug Metab Dispos *7 (6):* 373–377

Ding TL, Gambertoglio JG, Amend WJC, Birnbaum J, Benet LZ 1980 Azathioprine (AZA) bioavailability and pharmacokinetics in kidney transplant patients. Clin Pharmacol Ther *27 (2):* 250

Divoll M, Ameer B, Abernethy DR, Greenblatt DJ 1982 Age does not alter acetaminophen absorption. J Am Geriatr Soc *30 (4):* 240

Divoll M, Greenblatt DJ, Ochs HR, Shader RI 1983 Absolute bioavailability of oral and intramuscular diazepam: Effects of age and sex. Anesth Analg *62 (1):* 1–8

Dixon R, Carbone JJ, Mohacsi E, Perry C 1978 Dextromethorphan: Radioimmunoassay and pharmacokinetics in the dog. Res Commun Chem Pathol Pharmacol *22 (2):* 243–245

Dobrinska MR, Kukovetz W, Beubler E, Leidy HL, Gomez HJ, Demetriades J, Bolognese JA 1982 Pharmacokinetics of the pivaloyloxyethyl (POE) ester of methyldopa, a new prodrug of methyldopa. J Pharmacokinet Biopharm *10 (6):* 587–600

Doherty JE, Marcus FI, Binnion PF 1984 A multicenter evaluation of the absolute bioavailability of digoxin dosage forms. Curr Ther Res *35 (2):* 301–306

Doluisio JT (moderator) 1972 Panel discussion on case histories in bioavailability of drugs. Pharmacol *8:* 153–198

Doluisio JT, LaPiana JC, Wilkinson GR, Dittert LW 1969 Pharmacodynamic interpretation of dicloxacillin levels in serum after extravascular administration. Antimicrob Agents Chemother *9:* 49–55

Doluisio JT, Smith RB, Chun AH, Dittert LW 1978 Pentobarbital absorption from capsules and suppositories in humans. J Pharm Sci *67 (11):* 1586–1588

Dubruc C, Bianchetti G, Thenot JP, Thiercelin JF, Lambert B, Jacobs C, Warrington S, Abriol C 1987 Pharmacodynamic profile of cicloprolol, an original partial beta-adrenergic receptor agonist. Proc 3rd Eur Congr Biopharm Pharmacokinet Imp Reix Clermont-Ferrand p 335

Duchin KL, Singhvi SM, Willard D, Migdalof BH, McKinstry DN 1982 Captopril kinetics. Clin Pharmacol Ther *31 (4):* 452

Durand A, Burke JT, Tudela S, Thenot JP, Morselli PL 1987 A pharmacodynamic and distribution study of ifenprodil in the male rat following acute administration of the ^{14}C radiolabelled compound. Proc 3rd Eur Congr Biopharm Pharmacokinet Imp Reix Clermont-Ferrand p 253

Dusterberg B, Schmidt-Gollwitzer M, Humpel M 1985 Pharmacokinetics and biotransformation of estradiol valerate in ovariectomized women. Hormone Res *21 (3):* 145–154

D'Incalci M, Farina P, Sessa C, Mangioni C, Conter V, Masera G, Rocchetti M, Pisoni MB, Piazza E 1982 Pharmacokinetics of VP 16–213 given by different administration methods. Cancer Chemother Pharmacol *7 (2–3):* 141–145

Eadie MJ, Brophy TRO, Ohlrich G, Tyrer JH 1984 Dexamethasone: Pharmacokinetics in neurological patients. Clin Exp Neurol *20:* 107–118

Edgar B, Hoffmann KJ, Lundborg P, Regardh CG, Ronn O, Weidolf L 1985 Absorption, distribution, and elimination of felodipine in man. Drugs *29 (Suppl 2):* 9–15

Edwards DJ, Svensson CK, Visco JP, Lalka D 1982 Clinical pharmacokinetics of pethidine. Clin Pharmacokinet *7:* 421–433

Ehrnebo M 1974 Pharmacokinetics and distribution properties of pentobarbital in humans following oral and intravenous administration. J Pharm Sci *63 (7):* 1114–1118

Ehrnebo M, Boreus LO, Lonroth U 1977 Bioavailability and first pass metabolism of oral pentazocine in man. Clin Pharmacol Ther *22 (6):* 888–892

Ehrnebo M, Nilsson SO, Boreus LO Pharmacokinetics of ampicillin and its prodrugs bacampicillin and pivampicillin in man. J Pharmacokinet Biopharm. *7 (5):* 429–451

Eichelbaum M, Somogyi A, von Unruh GE, Dengler HJ 1981 Simultaneous determination of the intravenous and oral pharmacodynamic parameters of D, L-verapamil using stable isotope-labelled verapamil. Eur J Clin Pharmacol *19 (2):* 133–137

Elfstrom J, Lindgren S 1978 Influence of bed rest on the pharmacokinetics of phenazone. Eur J Clin Pharmacol *13:* 379–383

Elliott HL, Meredith PA, Sumner DJ, Reid JL 1984 a Comparison of the clinical pharmacokinetics and concentration-effect relationship for medroxalol and labetalol. Br J Clin Pharmacol *17:* 573–578

Elliott HL, Vincent J, Hughes DMA, Meredith PA, Reid JL 1984 b Trimazosin in normotensive subjects. Clin Pharmacol Ther *35:* 156–160

Else OF, Sorenson H, Edwards IR 1978 Plasma timolol levels after oral and intravenous administration. Eur J Clin Pharmacol *14:* 431–434

El-Rashidy R 1981 Estimation of the systemic bioavailability of timolol in man. Biopharm Drug Dispos *2 (2):* 197–202

El-Yazigi A, Sawchuk RJ 1981 Theophylline absorption and disposition in rabbits: Oral, intravenous, and concentration-dependent kinetic studies. J Pharm Sci *70 (4):* 452–456

Evard D, Aubry JP, Le Quintrec Y, Cheymol G, Cheymol A 1984 Study of the bioavailability of pindolol in malabsorption syndromes. Br J Clin Pharmacol *18 (4):* 632–637

Fabre J, Milek E, Kalfopoulos P, Merier G 1971 Tetracycline kinetics in the human being. Schweiz Med Wochenschr *101 (17):* 593–598

Faulkner JK, McGibney D, Chasseaud LF, Perry JL, Taylor IW 1986 The pharmacokinetics of amlodipine in healthy volunteers after single intravenous and oral doses and after 14 repeated oral doses given once daily. Br J Clin Pharmacol *22 (1):* 21–25

Finch RE, Bending MR, Lant AF 1979 Plasma levels of 5-fluorouracil after oral and intravenous administration in cancer patients. Br J Clin Pharmacol *7:* 613–617

Fitzgerald JD, Ruffin R, Smedstad KG, Roberts R, McAinsh J 1978 Studies on the pharmacokinetics and pharmacodynamics of atenolol in man. Eur J Clin Pharmacol *13 (2):* 81–89

Fix JA, Engle K, Porter PA, Leppert PS, Selk SJ, Gardner CR, Alexander J 1986 Acylcarnitines: Drug absorption-enhancing agents in the gastrointestinal tract. Am J Physiol *251:* G 332 – G 340

Fleuren HL, Thien TA, Verwey-van Wissen CP, van Rossum JM 1979 Absolute bioavailability of chlorthalidone in man: A cross-over study after intravenous and oral administration. Eur J Clin Pharmacol *15 (1):* 35–50

Flouvat B, Roux A, Chau NP, Viallet M, Andre-Fouet X, Woehrle R, Gregoire J 1981 Pharmacokinetics and bioavailability of diacetolol, the main metabolite of acebutolol. Eur J Clin Pharmacol *19 (4):* 287–292

Foord RD 1976 Cefuroxime: Human pharmacokinetics. Antimicrob Agents Chemother *9 (5):* 741–747

Forrest JA, Clements JA, Prescott LF 1982 Clinical pharmacokinetics of paracetamol. Clin Pharmacokinet *7 (2):* 93–107

Forsman, A, Ohman R 1976 Pharmacodynamic studies on haloperidol in man. Curr Ther Res *20 (3):* 319–336

Foster TS, Hamann SR, Richards VR, Bryant PJ, Graves DA, McAllister RG 1983 Nifedipine kinetics and bioavailability after single intravenous and oral doses in normal subjects. J Clin Pharmacol *23 (4):* 161–167

Franklin RA, Aldridge A 1976 Studies on the metabolism of meptazinol, a new analgesic drug. Br J Clin Pharmacol *3 (3):* 497–502

Frey HH, Loscher W 1980 Clinical pharmacokinetics of phenytoin in the dog: A reevalution. Am J Vet Res *41 (10):* 1635–1638

Frey HH, Rieh B 1981 Pharmacokinetics of naproxen in the dog. Am J Vet Res *42 (9):* 1615–1617

Fuccella LM, Corvi G, Moro E, Pogliani E, Tamassia V, Tosolini G 1979 Pharmacodynamic, bioavailability, and pharmacokinetic study of indobufen (K 3920), an inhibitor of platelet aggregation, after a single dose in man. Eur J Clin Pharmacol *15:* 323–327

Gaillot J, Le Roux Y, Cournot A, Duchier J, Frydman A 1987 Pharmacokinetics of metopimazine after single and repeated oral dose administration in young healthy subjects. Proc 3rd Eur Congr Biopharm Pharmacokinet Imp Reix Clermont-Ferrand p 354

Galiano A, Viega MD, Fernandez C, Cadorniga R 1987 Oxodipine: In vitro study in solid dispersions and pharmacodynamic. Proc 3rd Eur Congr Biopharm Pharmacokinet Imp Reix Clermont-Ferrand p 1102

Gammans RE, Mayol RF, LaBudde JA 1986 Metabolism and disposition of buspirone. Am J Med *80 (3 B):* 41–51

Garrett ER, Green JR, Bialer M 1982 Bretylium pharmacokinetics and bioavailabilities in man with various doses and modes of administration. Biopharm Drug Dispos *3 (2):* 129–136

Garrett ER, Van Peer A, Altmayer P, Schuermann W, Lucker P 1982 Pharmacokinetics of the immunomodulatory 1, 2-0-isopropylidene-3-0-3'-(N',N'-dimethyl-amino-n-propyl)-D-glucofuranose HCl in normal human volunteers. J Pharmacokinet Biopharm *10 (3):* 247–264

Garrett ER, Roseboom H, Green JR, Schuermann W 1983 Pharmacokinetics of papaverine hydrochloride and the biopharmaceutics of its oral dosage forms. Int J Clin Pharmacol Biopharm *16 (5):* 193–208

George CF 1979 Drug kinetics and hepatic blood flow. Clin Pharmacokinet 4: 433–448

Gibaldi M, Perrier D 1982 Absorption kinetics and bioavailability. Pharmacokinetics. New York, NY: Marcel Dekker Inc 145–198

Gibaldi M, Boyes RN, Feldman S 1971 Influence of first-pass effect on availability of drugs on oral administration. J Pharm Sci *60 (9):* 1338–1340

Gilfrich HJ, Kremer G, Mohrke W, Mutschler E, Volger KD 1983 Pharmacokinetics of triamterene after i. v. administration to man: Determination of bioavailability. Eur J Clin Pharmacol *25:* 237–241

Gillis AM, Kates RE 1984 Clinical pharmacokinetics of the newer antiarrhythmic agents. Clin Pharmacokinet *9:* 375–403

Goa KL, Heel RC 1986 Zopiclone. A review of its pharmacokinetic and pharmacodynamic properties and therapeutic efficacy as an hypnotic. Drugs *32 (1):* 48–65

Goa KL, Sorkin M 1987 Nitrendipine. A review of its pharmacokinetic and pharmacodynamic properties and therapeutic efficacy in the treatment of hypertension. Drugs *33:* 123–155

Gommaa AA, Osman FH 1983 Influence of acetaminophen-induced hepatic necrosis on the pharmacokinetics of levonorgestrel. Contraception *28 (2):* 149–157

Gourlay GK, Cherry DA, Cousins MJ 1986 A comparative study of the efficacy and pharmacokinetics of oral methadone and morphine in the treatment of severe pain in patients with cancer. Pain *25 (3):* 297–312

Graffner C, Johnsson G, Sjogren J 1975 Pharmacokinetics of procainamide intravenously and orally as conventional and slow-release tablets. Clin Pharmacol Ther *17 (4):* 414–423

Graffner C, Lagerstrom PO, Lundborg P, Ronn O 1979 Pharmacokinetics of metoclopramide intravenously and orally determined by liquid chromatography. Br J Clin Pharmacol *8 (5):* 469–474

Graham DJM, Dow RJ, Hall DJ, Alexander OF, Mroszczak EJ, Freedman D 1985 The metabolism and pharmacokinetics of nicardipine hydrochloride in man. Br J Clin Pharmacol *20 (Suppl 1):* 23 S – 28 S

Grahnen A, Seideman P, Lindstrom B, Haglund K, von Bahr C 1981 Prazosin kinetics in hypertension. Clin Pharmacol Ther *30 (4):* 439–446

Grahnen A, Hammarlund M, Lundqvist T 1984 Implications of intraindividual variability in bioavailability studies of furosemide. Eur J Clin Pharmacol *27 (5):* 595–602

Gram LF, Overo KF 1975 First-pass metabolism of nortriptyline in man. Clin Pharmacol Ther *18:* 305–314

Grebow PE, Treitman JA 1981 Pharmacokinetics of indapamide in dogs. J Pharm Sci *70 (12):* 1310–1312

Green AW, Ebling WF, Gardner MJ, Jusko WJ 1984 Cimetidine methyl-prednisolone-theophylline metabolic interaction. Am J Med *77 (6):* 1115–1118

Greenblatt DJ 1981 Clinical pharmacokinetics of oxazepam and lorazepam. Clin Pharmacokinet *6:* 89–105

Greenblatt DJ, Pfeifer HJ, Ochs HR, Franke K, MacLaughlin DS, Smith TW, Koch-Weser J 1977 Pharmacokinetics of quinidine in humans after intravenous, intramuscular, and oral administration. J Pharmacol Exp Ther *202 (2):* 365–378

Greenblatt DJ, Shader RI, MacLeod SM, Sellers EM 1978 Clinical pharmacokinetics of chlordiazepoxide. Clin Pharmacokinet *3: 381–394*

Greenblatt DJ, Shader RI, Franke K, MacLaughlin DS, Harmatz JS, Allen MD, Werner A, Woo E 1979 Pharmacokinetics and bioavailability of intravenous, intramuscular, and oral lorazepam in humans. J Pharm Sci *68 (1):* 57–63

Greenblatt DJ, Divoll M, Harmatz JS, Shader RI 1982 Pharmacodynamic comparison of sublingual lorazepam with intravenous, intramuscular, and oral lorazepam. J Pharm Sci *71:* 248–252

Greenblatt DJ, Divoll M, Abernethy DR, Ochs HR, Shader RI 1983 Clinical pharmacokinetics of the newer benzodiazepines. Clin Pharmacokinet *8:* 233–252

Grimaldi R, Perucca E, Ruberto G, Gelmi C, Trimarchi F, Hollmann M, Crema A 1986 Pharmacodynamic and pharmacokinetic studies following the intravenous and oral administration of the antiparkinsonian drug biperiden to normal subjects. Eur J Clin Pharmacol *29 (6):* 735–737

Grochow LB, Colvin M 1979 Clinical pharmacokinetics of cyclophosphamide. Clin Pharmacokinet *4:* 380–394

Grossi G, Sturani C, Battistoni R 1985 Pharmacokinetics of mepixanox after oral and intravenous administration. Curr Ther Res *38 (1):* 141–146

Guentert TW, Holford NH, Coates PE, Upton RA, Riegelman S 1979 Quinidine pharmacokinetics in man: Choice of a disposition model and absolute bioavailability studies. J Pharmacokinet Biopharm *7 (4):* 315–330

Gugler R, van Unruh GE 1980 Clinical pharmacokinetics of valproic acid. Clin Pharmacokinet *5:* 67–83

Gugler R, Manion CV, Azarnoff DL 1976 Phenytoin: Pharmacokinetics and bioavailability. Clin Pharmacol Ther *19 (2):* 135–142

Gunnarsson PO, Andersson SB, Johansson SA, Nilsson T, Plym-Forshell G 1984 Pharmacokinetics of estramustine phosphate (estracyst) in prostatic cancer patients. Eur J Clin Pharmacol *26 (1):* 113–119

Gustafsson LL, Walker O, Alvan G, Beermann B, Estevez F, Gleisner L, Lindstrom B, Sjoqvist F 1983 Disposition of chloroquine in man after single intravenous and oral doses. Br J Clin Pharmacol *15 (4):* 471–479

Hager WD, Mayersohn M, Graves PE 1981 Digoxin bioavailability during quinidine administration. Clin Pharmacol Ther *30 (5):* 594

Harris PA, Riegelman S 1969 Influence of the route of administration on the area under the plasma concentration-time curve. J Pharm Sci *58 (1):* 71–75

Hartvig P, Roos BE, Ahs U, Ryde M 1981 Pharmacokinetics of propiomazine following intravenous, intramuscular, and oral administration with special reference to the elimination phase. Curr Ther Res Clin Exp *29:* 351–362

Harvey VJ, Slevin ML, Woollard RC, Johnston A, Barnett MJ, Wrigley PF, Turner P 1984 The bioavailability of oral intermediate-dose methotrexate. Cancer Chemother Pharmacol *13 (2):* 91–94

Haskins NJ, Ford GC, Grigson SJW, Palmer RF 1978 Bioavailability using cold labels: Studies on a novel antidiarrhoeal agent SC-27166. In: *Baille TA (ed)* Stable Isotopes, University Park Press pp 127–138

Haskins NJ, Wadell KA, Ford GC, Spalton PN, Walls CM, Forrest TJ, Palmer RF 1980 The absorption of disopyramide in animals determined using a stable isotope co-administration technique. Biomed Mass Spectrom *7 (2):* 80–83

Heeg JF, Hiser MF, Satonin DK, Rose JQ 1984 Pharmacokinetics of probucol in male rats. J Pharm Sci *73 (12):* 1758–1763

Heinzow B, Corbett H, Constantinides S, Bourne R, McLean AJ 1984 Interaction between oral hydralazine and propranalol. J Pharmacol Exp Ther *229 (2):* 509–514

Henderson GL, North-Root H, Kuttab SH 1977 Metabolism and disposition of 1-alpha-acetylmethadol in the rat. Drug Metab Dispos *5 (4):* 321–328

Hengstmann JH, Goronzy J 1982 Pharmacokinetics of ^{3}H-phenylephrine in man. Eur J Clin Pharmacol *21 (4):* 335–340

Hengstmann JH, Konen W, Konen C, Eichelbaum M, Bengler HJ 1975a Bioavailability of m-octopamine in man related to its metabolism. Eur J Clin Pharmacol *8:* 33–39

Hengstmann JH, Weyand U, Dengler HJ 1975 b The physiological disposition of etilefrine in man. Eur J Clin Pharmacol *9 (2–3):* 179–187

Hengy H, Kolle EU, Kohl W, Vollmer KO 1987 Pharmacokinetics of the new calcium antagonist GO-5438 in dogs. Proc 3rd Eur Congr Biopharm Pharmacokinet Imp Reix Clermont-Ferrand p 265

Hermann P, Morselli PL 1985 Pharmacokinetics of diltiazem and other calcium entry blockers. Acta Pharmacol Toxicol *57 (Suppl II):* 10–20

Hermann P, Rodger SD, Remones G, Thenot JP, London DR, Morselli PL 1983 Pharmacokinetics of diltiazem after intravenous and oral administration. Eur J Clin Pharmacol *24:* 349–352

Herman RJ, McAllister CB, Branch RA, Wilkinson GR 1985 Effects of age on meperidine disposition. Clin Pharmacol Ther *37 (1):* 19–24

Heykants J, Hendriks R, Meuldermans W, Michiels M, Scheygrond H, Reyntjens H 1981 On the pharmacokinetics of domperidone in animals and man. Eur J Drug Metab Pharmacokinet *6 (1):* 61–70

Higuchi S, Shiobara Y 1980 Comparative pharmacokinetics of nicardipine hydrochloride, a new vasodilator, in various species. Xenobiotica *10 (6):* 447–454

Hinderling PH, Garrett ER, Wester RC 1977 Pharmacokinetics of beta-methyldigoxin in healthy humans II. Oral studies and bioavailability. J Pharm Sci *66 (3):* 314–325

Hirai S, Hussain A, Haddadin M, Smith RB 1981 First-pass metabolism of ethinyl estradiol in dogs and rats. J Pharm Sci *70 (4):* 403–406

Hirji MR, Measuria H, Kuhn S, Mucklow JC 1985 Comparative study of the bioavailability of five different preparations. J Pharm Pharmacol *37:* 570–572

Hoffken G, Lode H, Prinzing C, Borner K, Koeppe P 1985 Pharmacokinetics of ciprofloxacin after oral and parenteral administration. Antimicrob Agents Chemother *27 (3):* 375–379

Hogstedt S, Lindberg B, Peng DR, Regardh CG, Rane A 1985 Pregnancy-induced increase in metoprolol metabolism. Clin Pharmacol Ther *37 (6):* 688–692

Holazo AA, Colburn WA, Gustafson JH, Young RL, Parsonnet M 1984 Pharmacokinetics of bumetanide following intravenous, intramuscular, and oral administration to normal subjects. J Pharm Sci *73 (8):* 1108–1113

Holford NHG 1986 Clinical pharmacokinetics and pharmacodynamics of warfarin. Understanding the dose-effect relationship. Clin Pharmacokinet *11:* 483–504

Holley FO, Magliozzi JR, Stanski DR, Lombrozo L, Hollister LE 1983 Haloperidol kinetics after oral and intravenous doses. Clin Pharmacol Ther 33 (4): 477–484

Homeida M, Jackson L, Roberts CJ 1978 Decreased first-pass metabolism of labelatol in chronic liver disease. Br Med J *2 (6144):* 1048–1050

Hooper WD, Kunze HE, Eadie MJ 1981 Pharmacokinetics and bioavailability of methylphenobarbital in man. Ther Drug Monit *3 (1):* 39–44

Houghton GW, Thorne PS, Smith J, Templeton R, Collier J 1979 Comparison of the pharmacokinetics of metronidazole in healthy female volunteers following either a single oral or intravenous dose. Br J Clin Pharmacol *8 (4):* 337–341

Houin G, Barre J, Tillement JP 1984 Absolute intramuscular, oral, and rectal bioavailability of alizapride. J Pharm Sci *73 (10):* 1450–1453

Huang SM, Huang YC, Chiou WL 1981 Oral absorption and presystemic first pass effect of chlorpheniramine in rabbits. J Pharmacokinet Biopharm *9 (6):* 725–738

Huang SM, Athanikar NK, Sridhar K, Huang YC, Chiou WL 1982 Pharmacokinetics of chlorpheniramine after intravenous and oral administration in normal adults. Eur J Clin Pharmacol *22 (4):* 359–360

Hucker HB, Stauffer SC, Albert KS, Lei BW 1977 Plasma levels and bioavailability of cyclobenzaprine in human subjects. J Clin Pharmacol *17 (11–12):* 719–727

Hull JH, Findlay JW, Rogers JF, Welch RM, Butz RF, Bustrack JA 1982 An evaluation of the effects of smoking on codeine pharmacokinetics and bioavailability in normal human volunteers. Drug Intell Clin Pharm *16 (11):* 849–854

Hultquist C, Lindberg C, Nyberg L, Kjellman B, Wettrell G 1984 Kinetics of terbutaline in asthmatic children. Eur J Respir Dis *134 (Suppl):* 195–203

Humpel M, Wendt H, Pommerenke G, Weis C, Speck U 1978 Investigations of pharmacokinetics of levonorgestrel to specific consideration of a possible first-pass effect in woman. Contraception *17 (3):* 207–220

Humpel M, Nieuweboer B, Wendt H, Speck U 1979 Investigations of pharmacokinetics of ethinyloestradiol to specific consideration of a possible first-pass effect. Contraception *19 (4): 421–432*

Humpel M, Toda T, Oshino N, Pommerenke G 1981 The pharmacokinetics of lisuride hydrogen maleate in rat, rabbit, and rhesus monkey. Eur J Drug Metab Pharmacokinet *6 (3):* 207–219

Humpel M, Krause W, Hoyer GA, Wendt H, Pommerenke G 1984 The pharmacokinetics and biotransformation of ^{14}C-lisuride hydrogen maleate in rhesus monkey and in man. Eur J Drug Metab Pharmacokinet *9 (4):* 347–357

Hupin C, de Suray JM, Versluys J, Lorent M, Dodion L, Lesne M 1979 Bioavailability study of gitoxin in a solid dosage form. Int J Clin Pharmacol Biopharm *17 (5):* 197–204

Hussain A, Hirai S, Bawarshi R 1980 Nasal absorption of propranolol from different dosage forms by rats and dogs. J Pharm Sci *69 (12):* 1411–1413

Huupponen R, Lammintausta R 1981 Chlorpropamide bioavailability and pharmacokinetics. Int J Clin Pharmacol Ther Toxicol *19 (7): 331–333*

Ibraheem JJ, Paalzow L, Tfelt-Hansen P 1983 Low bioavailability of ergotamine tartrate after oral and rectal administration in migraine sufferers. Br J Clin Pharmacol *16 (6):* 695–699

Imbimbo BP, Daniotti S, Vidi A, Foschi D, Saporiti F, Ferrante L 1986 Discontinuous oral absorption of cimetropium bromide, a new antispasmodic drug. J Pharm Sci *75 (7):* 680–684

Ingvast-Larsson C, Paalzow G, Paalzow L, Ottosson T, Lindholm A, Appelgren LE 1985 Pharmacodynamic studies of theophylline in horses. J Vet Pharmacol Ther *8 (1):* 76–81

Iwamoto K, Takei M, Watanabe J 1982 Gastrointestinal and hepatic first pass metabolism of aspirin in rats. J Pharm Pharmacol *34 (3):* 176–180

Jaillon P 1980 Clinical pharmacokinetics of prazosin. Clin Pharmacokinet *5 (4):* 365–376

Jansson R, Lindstrom B, Dahlberg PA Pharmacodynamic properties and bioavailability of methimazole. Clin Pharmacokinet *10:* 443–450

Janzen N, Berg B, Engels U, Huber HJ, Stanislaus F 1987 Pharmacokinetics and metabolism of the new antiestrogenic antitumor substance droloxifene in female rats. Proc 3rd Eur Congr Biopharm Pharmacokinet Imp Reix Clermont-Ferrand p 269

Jochemsen R, Hogendoorn JJ, Dingemanse J, Hermans J, Boeijinga JK, Breimer DD 1982 Pharmacokinetics and bioavailability of intravenous, oral, and rectal nitrazepam in humans. J Pharmacokinet Biopharm *10 (3):* 231–245

Jochemsen R, Nandi KL, Corless D, Wesselman JGJ, Breimer DD 1983 a Pharmacokinetics of brotizolam in the elderly. Br J Clin Pharmacol *16 (Suppl 2):* 299 S – 307 S

Jochemsen R, Wesselman JG, Hermans J, van Boxtel CJ, Breimer DD 1983 b Pharmacokinetics of brotizolam in healthy subjects following intravenous and oral administration. Br J Clin Pharmacol *16 (Suppl 2):* 285 S – 290 S

Johno I, Bialer M, Nickelson SA, Levy RH 1984 Disposition of progabide and valproic acid following intraperitoneal administration in rhesus monkey. Epilepsia *25 (5):* 578–585

Johnsson G, Regardh CG 1976 Clinical pharmacokinetics of beta-adrenoceptor blocking drugs. Clin Pharmacokinet *1:* 233–263

Johnsson G, Regardh CG, Solvell L 1975 Combined pharmacodynamic and pharmacokinetic studies in man of the adrenergic beta-receptor antagonist metoprolol. Acta Pharmacol Toxicol *36 (Suppl V):* 31–44

Jollow DJ, Brodie BB 1972 Mechanisms of drug absorption and of drug solution. Pharmacol *8:* 21–32

Jonkman JH, Berg WC, Schoenmaker R, de Zeeuw RA, Greving JE, Orie NG 1980 Disposition and clinical pharmacokinetics of microcrystalline theophylline. Eur J Clin Pharmacol *17 (5):* 379–384

Jordo L, Attman PO, Aurell M, Johansson L, Johnsson G, Regardh CG 1980 Pharmacodynamic and pharmacokinetic properties of metoprolol in patients with impaired renal function. Clin Pharmacokinet *5:* 169–180

Jorgensen A 1980 Pharmacodynamic studies in volunteers of intravenous and oral cis-(Z)-flupentixol and intramuscular cis-(Z)-flupentixol decanoate in viscoleo (R). Eur J Clin Pharmacol *18:* 355–360

Jorgensen A, Andersen J, Bjorndal N, Dencker SJ, Lundin L, Malm U 1982 Serum concentrations of cis-(Z)-flupentixol and prolactin in chronic schizophrenic patients treated with flupentixol and cis-(Z)-flupentixol decanoate. Psychopharmacology *77 (1):* 58–65

Juhran VW, Haase W, Gotz R, Fleissig W 1975 The pharmacokinetics of papaverine and its bioavailability from a sustained action preparation. Arzneimittelforschung *25 (5):* 771–773

Julou L, Guyonnet JC, Ducrot R, Fournel J, Pasquet J 1976 Ketoprofen (19.583 R.P.) (2-(3-benzoylphenyl)-propionic acid). Main pharmacological properties – Outline of toxicological and pharmacodynamic data. Scand J Rheumatol *14 (Suppl):* 33–44

Jusko WJ, Koup JR, Alvan G 1976 Nonlinear assessment of phenytoin bioavailability. J Pharmacokinet Biopharm *4 (4):* 327–336

Kamath BL, Yacobi A, Bupta SD, Stampfli H, Durrani M, Lai CM 1981 Bioavailability of N-acetylprocainamide from mixed diet in rats. Res Commun Chem Pathol Pharmacol *32 (2):* 299–330

Kamiya A, Ogata H, Fung HL 1982 Rectal absorption of nitroglycerin in the rat: Avoidance of first-pass metabolism as a function of rectal length exposure. J Pharm Sci *71 (6):* 621–624

Kampmann JP, Hansen JM 1981 Clinical pharmacokinetics of antithyroid drugs. Clin Pharmacokinet *6:* 401–428

Kampmann JP, Mortensen HB, Bach B, Waldorff S, Kristensen MB, Hansen JM 1979 Kinetics of propylthiouracil in the elderly. Acta Med Scand *624 (Suppl):* 93–98

Kapil RP, Axelson JE, Ongley R, Price JDE 1984 Nonlinear bioavailability of metoclopramide in the rat: Evidence for saturable first-pass metabolism. J Pharm Sci *73 (2):* 215–218

Kaplan SA, Weinfeld RE, Abruzzo CW, Lewis M 1972 Pharmacodynamic profile of sulfisoxazole following intravenous, intramuscular, and oral administration to man. J Pharm Sci *61 (5):* 773–778

Karim A, Kook C, Zitzewitz DJ, Zagarella J, Doherty M, Campion J 1976 Species differences in the metabolism and disposition of spironolactone. Drug Metab Dispos *4 (6):* 547–555

Karim A, Kook C, Novotney RL, Zagarella J, Campion J 1978 Pharmacokinetics and steady-state myocardial uptake of disopyramide in the dog. Drug Metab Dispos *6 (3):* 338–345

Karlen B, Andersson KE, Ekman G, Stromberg S, Ulmsten U 1982 Pharmacokinetics of terodiline in human volunteers. Eur J Clin Pharmacol *23 (3):* 267–270

Kauffman RE, Thirumoorthi MC, Buckley JA, Aravind MK, Dajani AS 1981 Relative bioavailability of intravenous chloramphenicol succinate and oral chloramphenicol palmitate in infants and children. J Pediatr *99 (6):* 963–967

Kaye B, Cussans NJ, Faulkner JK, Stopher DA, Reid JL 1986 The metabolism and kinetics of doxazosin in man, mouse, rat, and dog. Br J Clin Pharmacol *21 (Suppl 1):* 19 S – 25 S

Kleinbloesem CH, van Brummelen P, Van Harten J, Danhof M, Breimer DD 1985 Nifedipine: Influence of renal function on pharmacodynamic/hemodynamic relationship. Clin Pharmacol Ther *37 (5):* 563–574

Klippert PJ, Hulshoff A, Mingels MJ, Hofman G, Noordhoek J 1983 Low oral bioavailability of hexamethylmelamine in the rat due to simultaneous hepatic and intestinal metabolism. Cancer Res *43 (7):* 3160–3164

Klotz U, Antonin KH 1977 Pharmacokinetics and bioavailability of sodium valproate. Clin Pharmacol Ther *21 (6):* 736–743

Klotz U, Ziegler G 1982 Physiologic and temporal variation in hepatic elimination of midazolam. Clin Pharmacol Ther *32 (1):* 107–112

Klotz U, Muller-Seydlitz P, Heimburg P 1978 Pharmacokinetics of lorcainide in man: A new antiarrhythmic agent. Clin Pharmacokinet *3 (5):* 407–418

Klotz U, Muller-Seydlitz P, Heimburg P 1979 Disposition and antiarrhythmic effect of lorcainide. Int J Clin Pharmacol Biopharm *17 (4):* 152–158

Knodell RG, Spector MH, Brooks DA, Keller FX, Kyner WT 1980 Alterations in pentobarbital pharmacokinetics in response to parenteral and enteral alimentation in the rat. Gastroenterology *79 (16):* 1211–1216

Kohno K, Takeuchi Y, Etho A, Noda K 1977 Pharmacokinetics and bioavailability of diltiazem (crd-401) in dog. Arzneimittelforschung *27 (7):* 1424–1428

Koup JR, Williams-Warren J, Viswanathan CT, Weber A, Smith AL 1986 Pharmacokinetics of rifampin in children II. Oral bioavailability. Ther Drug Monit *8 (1):* 17–22

Kramer WG, Rensimer ER, Ericsson CD, Pickering LK 1984 Comparative bioavailability of intravenous and oral chloramphenicol in adults. J Clin Pharmacol *24:* 181–186

Krasny HC, de Miranda P, Blum MR, Elion GB 1981 Pharmacokinetics and bioavailability of acyclovir in the dog. J Pharmacol Exp Ther *216 (2):* 281–288

Krause W, Kuhne G 1983 Pharmacokinetics of mepindolol sulfate in the rat, dog, and rhesus monkey. Studies on species differences. Drug Metab Dispos *11 (2):* 91–96

Krause W, Krais T 1986 Pharmacokinetics and pharmacodynamics of the prostacyclin analog iloprost in man. Eur J Clin Pharmacol *30 (1):* 61–68

Krause W, Karras J, Seifert W 1983 a Pharmacokinetics of canrenone after oral administration of spironolactone and intravenous injection of canrenoate-K in healthy man. Eur J Clin Pharmacol 25 (4): 449–453

Krause W, Kuhne G, Schillinger E 1983 b Pharmacokinetics and biotransformation of methane sulphonanilides with anti-inflammatory activitiy in the rat and monkey – comparison with piroxicam. Xenobiotica *13 (5):* 265–272

Kreuter J, Higuchi T 1979 Improved delivery of methoxsalen. J Pharm Sci *68 (4): 451–454*

Kukovetz WR, Beubler E, Kreuzig F, Moritz AJ, Nirnberger G, Werner-Breitenecker L 1983 Bioavailability and pharmacokinetics of D-penicillamine. J Rheumatol *10 (1):* 90–94

Kwan KC, Till AE 1973 Novel method for bioavailability assessment. J Pharm Sci *62 (9):* 1494–1497

Lagas M, Jonkman JH 1985 Influence of food on the rate and extent of absorption of theophylline after single dose oral administration of a controlled release tablet. Int J Clin Pharmacol Ther Toxicol *23 (8):* 424–426

Lalka D, Meyer MB, Duce BR, Elvin AT 1976 Kinetics of the oral antiarrhythmic lidocaine congener, tocainide. Clin Pharmacol Ther *19 (6):* 757–766

Lane EA, Levy RH 1983 Pharmacodynamic relationships between cinromide and its metabolites in the rhesus monkey. I. 3-Bromocinnamamide, an active metabolite. J Pharm Sci *72 (5):* 493–496

Laskin OL 1983 Clinical pharmacokinetics of acyclovir. Clin Pharmacokinet *8:* 187–201

Latini R, Tognoni G, Kates RE 1984 Clinical pharmacokinetics of amiodarone. Clin Pharmacokinet *9 (2):* 136–156

Lau HS, Hyneck ML, Berardi RR, Swartz RD, Smith DE 1986 Kinetics, dynamics, and bioavailability of bumetanide in healthy subjects and patients with chronic renal failure. Clin Pharmacol Ther *39 (6):* 635–645

Lauroba J, Domenech J, Moreno J, Pla-Delfina JM 1986 Relationships between biophasic disposition and pharmacodynamic behavior in nonsteroid antiinflammatory drugs. Arzneimittelforschung *36 (4):* 710–714

Lavene D, Weiss YA, Safar ME, Loria Y, Agorus N, Georges D, Milliez PL 1977 Pharmacokinetics and hepatic extraction ratio of pindolol in hypertensive patients with normal and impaired renal function. J Clin Pharmacol *17 (8–9):* 501–508

Lee MG, Chiou WL 1983 Evalution of potential causes for the incomplete bioavailability of furosemide: Gastric first-pass metabolism. J Pharmacokinet Biopharm *11 (6):* 623–640

Lee TG, Goldberg AD, Chang T, Serkland MT, Yakatan GJ 1983 Pharmacokinetics and efficacy of pirmenol hydrochloride in the treatment of ventricular dysrhythmia. J Cardiovasc Pharmacol *5 (4):* 632–637

Leitold VM, Laufen H 1983 Comparative antianginal, haemodynamic, and pharmacodynamic effect of isosorbide 2-mononitrate and isosorbide dinitrate in the rat. Arzneimittelforschung *74 (8):* 1117–1121

Lemanowicz EF, Sugita ET, Niebergall PJ, Schnaare RL 1979 Kinetics of absorption and elimination of pralidoxime chloride in dogs. J Pharm Sci *68 (2):* 141–145

Leonard RG, Talbert RL 1982 Calcium-channel blocking agents. Clin Pharm *1 (1):* 17–33

Lesne M, Clerckx-Braun F 1981 Study of the pharmacodynamic parameters of a new diuretic, torasemide, administered by oral and intravenous routes to human subjects. Proc 1st Eur Congr Biopharm Pharmacokinet p 61–67

Lettieri J, Fung HL 1976 Absorption and first-pass metabolism of ^{14}C-gamma-hydroxybutyric acid. Res Commun Chem Pathol Pharmacol *13 (3):* 425–430

Liedholm H, Liden A, Kroon L, Melander A, Wahlin-Boll E 1985 Pharmacokinetics of dixyrazine: Low bioavailability, improved by food intake. Drug Nutr Interact *3:* 87–92

Lima JJ, Haughey DB, Leier CV 1984 Disopyramide pharmacokinetics and bioavailability following simultaneous administration of disopyramide and ^{14}C-disopyramide. J Pharmacokinet Biopharm *12:* 289–313

Lindberg RL, Sellman RL, Iisalo E 1985 First-pass metabolism of nomifensine in dogs. Eur J Drug Metab Pharmacokinet *10 (1):* 21–25

Lindberg RL, Syvalahti EK, Pihlajamaki KK 1986 Disposition of nomifensine after acute and prolonged dosing. Clin Pharmacol Ther *39 (4):* 384–388

Ling T 1984 Pharmacokinetics of nicardipine following oral and intravenous administration in man. Postgrad Med J *60 (Suppl 4):* 7–10

Little PJ, Jennings GL, Skews H, Bobik A 1982 Bioavailability of dihydroergotamine in man. Br J Clin Pharmacol *13 (6):* 785–790

Lo MW, Effeney DJ, Pond SM, Silber BM, Reigelman S 1982 Lack of gastrointestinal metabolism of propranolol in dogs after portacaval transposition. J Pharmacol Exp Ther *221 (2):* 512–515

Lo MW, Juergens GP, Whitney CC 1984 Determination of nalbuphine in human plasma by automated high-performance liquid chromatography with electrochemical detection. Res Commun Chem Pathol Pharmacol 43 (1): 159–168

Locniskar A, Greenblatt DJ, Zinny MA, Harmatz JS, Shader RI 1984 Absolute bioavailability and effect of food and antacid on diazepam absorption from a slow release preparation. J Clin Pharmacol *24 (5–6):* 255–263

Loos U, Musch E, Jensen JC, Mikus G, Schwabe HK, Eichelbaum M 1985 Pharmacokinetics of oral and intravenous rifampicin during chronic administration. Klin Wochenschr *63 (23):* 1205–1211

Loscher W, Frey HH 1981 Pharmacokinetics of diazepam in the dog. Arch Int Pharmacodyn Ther *254 (2): 180–195*

Louis WJ, Christophidis N, Brignell M, Vijayasekaran V, MacNeil J, Vajda FJ 1978 Labetalol: Bioavailability, drug plasma levels, plasma renin and catecholamines in acute and chronic treatment of resistant hypertension. Aust N Z J Med *8 (6):* 602–609

Love BL, Moore RG, Thomas J, Chaturvedi S 1981 Pharmacokinetics of zimelidine in humans – plasma levels and urinary

excretion of zimelidine and norzimelidine after intravenous and oral administration of zimelidine. Eur J Clin Pharmacol *20 (2):* 135–139

Ludden TM, McNay JL, Shepherd AMM, Lin MS 1982 Clinical pharmacokinetics of hydralazine. Clin Pharmacokinet *7: 185–205*

Lund L, Alvan G, Berlin A, Alexanderson B 1974 Pharmacokinetics of single and multiple doses of phenytoin in man. Eur J Clin Pharmacol *7 (2):* 81–86

Lund J, Christensen JA, Bechgaard E, Molander L, Larsson H 1979 Pharmacokinetics of femoxetine in man. Acta Pharmacol Toxicol *44 (3):* 177–178

MacGregor TR, Relihan GL, Keirns JJ 1985 Pharmacokinetics of oral sustained release clonidine in humans. Arzneimittelforschung *35 (1 A):* 440–446

Magnussen I, Nielsen-Kudsk F 1980 Bioavailability and related pharmacokinetics in man of orally administered L-5-hydroxytryptophan in steady state. Acta Pharmacol Toxicol *46 (4):* 257–266

Major RM, Taylor T, Chasseaud LF, Darragh A, Lambe RF 1984 Isosorbide-5-mononitrate kinetics. Clin Pharmacol Ther *35 (5):* 653–659

Manion CV, Lalka D, Baer DT, Meyer MB 1977 Absorption kinetics of procainamide in humans. J Pharm Sci *66 (7):* 981–984

Mantyla R, Kanto J 1981 Clinical pharmacokinetics of methylergometrine (methylergonovine). Int J Clin Pharmacol Ther Toxicol *19 (9):* 386–389

Marino EL, Dominguez-Gil A, Muriel C 1982 Influence of dosage form and administration route on the pharmacokinetics of cefadroxil. Int J Clin Pharmacol Ther Toxicol *20 (2):* 73–77

Martini A, Moro E, Marrari P, Pacciarini MA, Sega R, Dell'Osso L, Bertelli A, Tamassia V 1983 Pharmacokinetics and bioavailability of metergoline in healthy volunteers after single i. v. and oral administration. Int J Clin Pharmacol Res *3 (1):* 27–34

Marvola M, Kivirinta R 1978 Pharmacokinetics and locomotor activity increasing effect of ephedrine in mice. Acta Pharmacol Toxicol *43:* 381–386

Marzo A, Ghirardi P, Merlo L, Marchetti G 1977 Absorption, fate, and excretion of glaziovine-^{14}C in the dog. Arch Int Pharmacodyn Ther *227 (2):* 254–262

Mason, WD, Winer N 1976 Pharmacokinetics of oxprenolol in normal subjects. Clin Pharmacol Ther *20 (4):* 401–412

Mason WD, Winer N, Kochak G, Cohen I, Bell R 1979 Kinetics and absolute bioavailability of atenolol. Clin Pharmacol Ther *25 (4): 408–415*

Mas-Chamberlin C, Gillet G, Andre J, Gomeni R, Dring LG, Morselli PL 1981 The metabolism and kinetics of triflorex in the rat. Drug Metab Dispos *9 (2):* 150–155

Mather LE, Meffin PJ 1978 Clinical pharmacokinetics of pethidine. Clin Pharmacokinet *3:* 352–368

Mather LE, Austin KL, Philpot CR, McDonald PJ 1981 Absorption and bioavailability of oral erythromycin. Br J Clin Pharmacol *12 (2):* 131–140

Matsukura M, Higashi A, Ikeda T, Matsuda I 1981 Bioavailability of phenobarbital by rectal administration. Pediatr Pharmacol *1:* 259–265

Mattie H, Dijkmanns BAC, van Gulpen C 1982 The pharmacokinetics of metronidazole and tinidazole in patients with mixed aerobic-anaerobic infections. J Antimicrob Chemother *10 (Suppl A):* 59–64

Mattila J, Mannisto PT, Mantyla R, Nykanen S, Lamminsivu U 1983 Comparative pharmacokinetics of metronidazole and tinidazole as influenced by administration route. Antimicrob Agents Chemother *23 (5):* 721–725

McAllister RG, Kirsten EB 1982 Pharmacology of verapamil. Part 4. Kinetic and dynamic effects after single intravenous and oral doses. Clin Pharmacol Ther *31:* 418–426

McBurney A, Farrow PR, Ainsworth S, Ward JW 1985 Serum concentrations and urinary excretion of pinacidil and its major metabolite, pinacidil pyridine-N-oxide following i. v. and oral administration in healthy volunteers. Br J Clin Pharmacol *19:* 91–94

McDevitt DG, Nies AS, Wilkinson GR, Smith RF, Woosley RL, Oates JA 1976 Antiarrhythmic effects of a lorcainide congener, tocainide, 2-amino-2′, 6′-propionoxylidide, in man. Clin Pharmacol Ther *19 (4):* 396–402

McFadyen ML, Folb PI, Miller R, Marks IN, Moshal MG 1983 The pharmacokinetics of ranitidine in patients with chronic duodenal ulceration: A comparison of responders and non-responders. Eur J Clin Pharmacol *24:* 441–447

McGovern EM, Grevel J, Bryson SM 1986 Pharmacokinetics of high-dose metoclopramide in cancer patients. Clin Pharmacokinet *11:* 415–424

McGovren JP, Nelson KG, Lassus M, Cradock JC, Plowman J, Christopher JP 1984 Menogaril: A new anthracycline agent entering clinical trials. Invest New Drugs *2:* 359–367

McKiernan BC, Neff-Davis CA, Koritz GD, Davis LE, Pheris DR 1981 Pharmacodynamic studies of theophylline in dogs. J Vet Pharmacol Ther *4 (2):* 103–110

McNiel NO, Morgan LR 1981 The bioavailability of oral and intravenous ifosfamide in the treatment of bronchogenic carcinoma. Int J Clin Pharmacol Ther Toxicol *19 (11):* 490–493

Meacham RH, Chiang ST, Kick CJ, Sisenwine SF, Jusko WJ, Ruelius HW 1981 Pharmacodynamic disposition of guanabenz in the rhesus monkey. Drug Metab Dispos *9 (6):* 509–514

Mehvar R, Jamali F, Watson MWB, Skelton D 1987 Pharmacokinetics of tetrabenazine and its major metabolite in man and rat. Drug Metab Dispos *15 (2):* 250–255

Meier J 1982 Pharmacodynamic comparison of pindolol with other beta-adrenoceptor blocking agents. Am Heart J *104 (2 pt 2):* 364–373

Melander A, McLean A 1983 Influence of food intake on presystemic clearance of drugs. Clin Pharmacokinet *8 (4):* 286–296

Melgar MD, Zuleski FR, Malbica JO 1984 Metabolism, disposition, and pharmacokinetics of tracazolate in rat and dog. Drug Metab Dispos *12 (4):* 396–402

Meredith PA, Elliott HL, McSharry Dr, Kelman AW, Reid JL 1983 The pharmacokinetics of endralazine in essential hypertensives and in normotensive subjects. Br J Clin Pharmacol *16 (1):* 27–32

Meresaar U, Nilsson MI, Holmstrand J, Anggard E 1981 Single dose pharmacokinetics and bioavailability of methadone in man studied with a stable isotope method. Eur J Clin Pharmacol *20 (6):* 473–478

Miaskiewicz Sl, Shively CA, Vesell ES 1982 Sex differences in absorption kinetics of sodium salicylate. Clin Pharmacol Ther *31 (1):* 30–37

Mihaly GW, Ward SA, Edwards G, Nicholl DD, Orme ML, Breckenridge AM 1985 Pharmacokinetics of primaquine in man. I. Studies of the absolute bioavailability and effects of dose size. Br J Clin Pharmacol *19 (6):* 745–750

Miller R 1984 Pharmacokinetics and bioavailability of randitidine in humans. J Pharm Sci *73 (10):* 1376–1379

Misra AL, Bartolomeo JG, Bloch R, Mule SJ, Bates TR 1980 Pharmacokinetics and metabolism of nor-LAAM, the active metabolite of LAAM in acutely and chronically treated rhesus monkeys. J Pharmacol Exp Ther *214 (3):* 599–607

Morichau-Beauchant M, Houin G, Mavier P, Alexandre C, Dhumeaux D 1986 Pharmacokinetics and bioavailability of ranitidine in normal subjects and cirrhotic patients. Dig Dis Sci *31 (2):* 113–118

Morino A, Sasaki H, Mukai H, Sugiyami M 1986 Receptor-mediated model relating anticonvulsant effect to brain levels of camazepam in the presence of its active metabolites. J Pharmacokinet Biopharm *14 (3):* 309–321

Mroszczak EJ, Runkel R, Strand LJ, Tomlinson RV, Fratis A, Segre E 1978 Cloprednol bioavailability in humans. J Pharm Sci *67 (7):* 920–923

Murell GAC, Rapeport WG 1986 Clinical pharmacokinetics of allopurinol. Clin Pharmacokinet *11:* 343–353

Mutschler E, Gilfrich HJ, Knauf H, Mohrke W, Volger KD 1983 Pharmacokinetics of triamterene. Clin Exp Hypertens *5 (2):* 249–260

Myre E, Rugstad HE, Hansen T 1982 Clinical pharmacokinetics of methyldopa. Clin Pharmacokinet *7 (3):* 221–233

Nagy A, Johansson R 1975 Plasma levels of imipramine and desipramine in man after different routes of administration. Naunyn Schmiedeberg's Arch Pharmacol *290 (2–3):* 145–160

Nahata MC, Powell DA 1981 Bioavailability and clearance of chloramphenicol after intravenous chloramphenicol succinate. Clin Pharmacol Ther *30 (3):* 368–372

Nakashima M, Asano M, Ohguchi S, Hashmoto H, Seki K, Miyazaki M, Takenaka T 1984 Amosulalol, a combined alpha and beta adrenoceptor antagonist: Kinetics after intravenous and oral doses. Clin Pharmacol Ther *36 (4):* 436–443

Narang PK, Wilder R, Chatterji DC, Yeager RL, Gallelli JF 1983 Systemic bioavailability and pharmacokinetics of methylprednisolone in patients with rheumatoid arthritis. Biopharm Drug Dispos *4 (3):* 233–248

Nauta EH, Mattie H 1976 Dicloxacillin and cloxacillin: Pharmacokinetics in healthy and hemodialysis subjects. Clin Pharmacol Ther *20 (1):* 98–108

Needs CJ, Brooks PM 1985 Clinical pharmacokinetics of the salicylates. Clin Pharmacokinet *10 (2):* 164–177

Neff-Davis CA, Davis LE, Gillette EL 1981 Metronidazole: A method for its determination in biological fluids and its disposition kinetics in the dog. J Vet Pharmacol Ther *4 (2):* 121–127

Nelson E, Powell JR, Conrad K, Likes K, Byers J, Baker S, Perrier D 1982 Phenobarbital pharmacokinetics and bioavailability in adults. J Clin Pharmacol *22 (2–3):* 141–148

Neu HC, Srinivasan S, Francke EL, Ortiz-Neu C, Christenson JG 1983 Pharmacokinetics of amdinocillin and pivamdinocillin in normal volunteers. Am J Med *75 (2 A):* 60–64

Neuvonen PJ 1979 Bioavailability of phenytoin: Clinical pharmacodynamic and therapeutic implications. Clin Pharmacokinet *4:* 91–103

Neuvonen PJ 1983 Biovailability of phenytoin: Clinical pharmacokinetics and therapeutic implications. In: *Gibaldi M, Prescott L (eds)* Handbook of clinical pharmacokinetics ADIS Health Science Press. pp 24–38

Newburger J, Castracane VD, Moore PH, Williams MC, Goldzieher JW 1983 The pharmacokinetics and metabolism of ethinyl estradiol and its three sulfates in the baboon. Am J Obstet Gynecol *146 (1):* 80–87

Newell DR, Calvert AH, Harrap KR, McElwain TJ 1983 Studies on the pharmacokinetics of chlorambucil and prednimustine in man. Br J Clin Pharmacol *15:* 253–258

Niazi S, Vishnupad KS, Veng-Pedersen P 1983 Absorption and disposition characteristics of nitrofurantoin in dogs. Biopharm Drug Dispos *4:* 213–223

Nielsen-Kudsk F, Pedersen AK 1979 Pharmacokinetics of dipyridamole. Acta Pharmacol Toxicol *44:* 391–399

Nilsson MI, Anggard E, Holmstrand J, Gunne LM 1982 a Pharmacokinetics of methadone during maintenance treatment: Adaptive changes during the induction phase. Eur J Clin Pharmacol *22:* 343–349

Nilsson MI, Meresaar U, Anggard E 1982 b Clinical pharmacokinetics of methadone. Acta Anaesth Scand *74 (Suppl):* 66–69

Nilsson-Ehle I, Fellner H, Hedstrom SA, Nilsson-Ehle P, Sjovall J 1985 Pharmacokinetics of clavulanic acid, given in combination with amoxycillin, in volunteers. J Antimicrob Chemother *16 (4):* 491–498

Nishikawa T, Nagata O, Tanbo K, Yamada T, Takahara Y, Kato H, Yamamoto Y 1985 Absorption, excretion, and metabolism of tiquizium bromide in dogs. Xenobiotica *15 (12):* 1053–1060

Nitsche V, Mascher H 1982 The pharmacokinetics of valproic acid after oral and parenteral administration in healthy volunteers. Epilepsia *23 (2):* 153–162

Norbury HM, Franklin RA, Graham DF 1983 Pharmacokinetics of the new analgesic, meptazinol, after oral and intravenous administration to volunteers. Eur J Clin Pharmacol *25 (1):* 77–78

Nyberg L 1984 Pharmacodynamic parameters of terbutaline in healthy man. An overview. Eur J Respir Dis *134 (Suppl):* 149–160

Obach R, Menargues A, Valles JM 1984 The pharmacodynamic profile of carbidopa in dogs. J Pharm Pharmacol *36 (6):* 415–416

Ochs HR, Knuchel M 1984 Pharmacokinetics and absolute bioavailability of diltiazem in humans. Klin Wochenschr *62 (7):* 303

Ochs HR, Greenblatt DJ, Woo E 1980 Clinical pharmacokinetics of quinidine. Clin Pharmacokinet *5:* 150–168

Ochs HR, Otten H, Greenblatt DJ, Dengler HJ 1982 Diazepam absorption: Effects of age, sex, and Billroth gastrectomy. Dig Dis Sci *27 (3):* 225–230

Ogata H, Kawatsu Y, Maruyama Y, Machida K, Haga T 1985 Bioavailability and diuretic effect of furosemide during a long-term treatment of chronic respiratory failure. Eur J Clin Pharmacol *28 (1):* 53–59

Ogiso T, Iwaki M, Tamaki E 1983 Bioavailability of indomethacin calcium and magnesium, and effect of the salts on drug metabolizing enzyme activities in rats. J Pharmacobiodyn *6 (11):* 803–813

Okolicsanyi L, Venuti M, Orlando R, Lirussi F, Nassuato G, Benvenuti C 1982 Oral and intravenous pharmacokinetics of cimetidine in liver cirrhosis. Int J Clin Pharmacol Ther Toxicol *20 (10):* 482–487

Okolicsanyi L, Venuti M, Strazzabosco M, Orlando R, Nassuato G, Iemmolo RM, Lirussi F, Muraca M 1984 Oral and intravenous pharmacokinetics of ranitidine in patients with liver cirrhosis. Int J Clin Pharmacol Ther Toxicol *22 (6):* 329–332

Olsen H, Aune H, Lilleaasen P, Gullisken M, Bodd E, Morland J 1986 The effect of ethanol intake on propoxyphene absorption and biotransformation in dogs. Alcoholism (NY) *10 (4):* 393–396

Olsson B, Johansson M, Gabrielsson J, Bolme P 1987 Human pharmacokinetics of N-acetylcysteine. Proc 3rd Eur Congr Biopharm Pharmacokinet Imp Reix Clermont-Ferrand p 219

Orme MLE, Back DJ, Breckenridge AM 1983 Clinical pharmacokinetics of oral contraceptive steroids. Clin Pharmacokinet *8:* 95–136

Osman MA, Patel RB, Irwin DS, Crag WA, Welling PG 1982 Bioavailability of chlorothiazide from 50, 100, and 250 mg solution doses. Biopharm Drug Dispos *3 (2):* 89–90

Park GB, Kershner RP, Angellotti J, Williams RL, Edelson J 1983 Oral bioavailability and intravenous pharmacokinetics of amrinone in humans. J Pharm Sci *72:* 817–819

Patel VS, Kramer WG 1986 Allopurinol absorption from different sites of the rat gastrointestinal tract. J Pharm Sci *75 (3):* 275–277

Paton DM, Webster DR 1985 Clinical pharmacokinetics of H1-receptor antagonists (the antihistamines). Clin Pharmacokinet *10 (6):* 477–497

Paxton JW 1986 The effect of food on the bioavailability and kinetics of the anticancer drug amsacrine and a new analog, N-5-dimethyl-9-[(2-methoxy-4-methylsulphonylamino)-phenylamino]-4-acridinecarboxamide in rabbits. J Pharm Pharmacol *38:* 837–840

Pedersen AK, FitzGerald GA 1984 Dose related kinetics of aspirin: Presystemic acetylation of platelet cyclooxygenase. N Engl J Med *311:* 1206–1211

Pedersen KE, Christiansen BD, Klitgaard NA, Nielsen-Kudsk F 1983 Effect of quinidine on digoxin bioavailability. Eur J Clin Pharmacol *24 (1):* 41–47

Pentikainen PJ, Neuvonen PJ, Tarpila S, Syvalahti E 1978 Effect of cirrhosis of the liver on the pharmacokinetics of chlormethiazole. Br Med J *2:* 861–863

Pentikainen PJ, Neuvonen PJ, Penttila A 1979 Pharmacokinetics of metformin after intravenous and oral administration to man. Eur J Clin Pharmacol *16 (3):* 195–202

Perrin VL 1985 Clinical pharmacokinetics of ergotamine in migraine and cluster headache. Clin Pharmacokinet *10 (4):* 334–352

Peterslund NA, Esmann V, Ipsen J, Dencker Christensen K, Munck Petersen C 1984 Oral and intravenous acyclovir are equally effective in herpes zoster. J Antimicrob Chemother *14:* 185–189

Pfeffer M, Gaver RC, Ximenez J 1983 Human intravenous pharmacokinetics and absolute oral bioavailability of cefatrizine. Antimicrob Agents Chemother *24 (6):* 915–920

Philipson A, Stiernstedt G, Ehrnebo M 1987 Comparison of the pharmacokinetics of cephradine and cefazolin in pregnant and non-pregnant women. Clin Pharmacokinet *12:* 136–144

Phillips TA, Howell A, Grieve RJ, Welling PG 1980 Pharmacokinetics of oral and intravenous fluorouracil in humans. J Pharm Sci *69:* 1428–1431

Pickup ME 1979 Clinical pharmacokinetics of prednisone and prednisolone. Clin Pharmacokinet *4:* 111–128

Pieters FAJM, Zuidema J 1987 The absolute bioavailability of dapsone in dogs and humans. Proc 3rd Eur Congr Biopharm Pharmacokinet Imp Reix Clermont-Ferrand p 2111

Pilbrant A, Schannong M, Vessman J 1981 Pharmacokinetics and bioavailability of tranexamic acid. Eur J Clin Pharmacol *20 (1):* 65–67

Pisani F, Richens A 1983 Pharmacokinetics of phenylethylmalonamide (PEMA) after oral and intravenous administration. Clin Pharmacokinet *8:* 272–276

Pisani F, Fazio A, Spina E, Artesi C, Pisani B, Russo M, Trio R, Perucca E 1986 Pharmacokinetics of the antidepressant drug viloxazine in normal subjects and in epileptic patients receiving chronic anticonvulsant treatment. Psychopharmacology *90 (3):* 295–298

Pond SM, Kretschzmar KM 1981 Effect of phenytoin on meperidine clearance and normeperidine formation. Clin Pharmacol Ther *30:* 680–686

Pond SM, Tozer TN 1984 First-pass elimination. Basic concepts and clinical consequences. Clin Pharmacokinet *9:* 1–25

Pourbaix S, Berger Y, Desager JP, Pacco M, Harvengt C 1985 Absolute bioavailability of amiodarone in normal subjects. Clin Pharmacol Ther *37 (2):* 118–123

Ptachcinski RJ, Venkataramanan R, Rosenthal JT, Burckart GJ, Taylor RJ, Hakala TR 1985 Cyclosporine kinetics in renal transplantation. Clin Pharmacol Ther *38 (3):* 296–300

Ptachcinski RJ, Venkataramanan R, Burckart GJ 1986 Clinical pharmacokinetics of cyclosporin. Clin Pharmacokinet *11 (2):* 107–132

Puozzo C, Rostin M, Montastruc JL, Houin G 1987 Absolute bioavailability study of midalcipran (F 2207) in volunteers. Proc 3rd Eur Congr Biopharm Pharmacokinet Imp Reix Clermont-Ferrand p 1103

Raaflaub J 1975 On the pharmacokinetics of chlorprothixene in man. Experientia *31 (5):* 557–558

Raaflaub J, Dubach UC 1975 On the pharmacokinetics of phenacetin in man. Eur J Clin Pharmacol *8:* 261–265

Raaflaub J, Haefelfinger P, Trautmann KH 1984 Single-dose pharmacokinetics of the MAO-inhibitor moclobemide in man. Arzneimittelforschung *34 (1):* 80–82

Rabin HR, Urtasun RC, Partington J, Koziol D, Sharon M, Walker K 1980 High dose metronidazole: Pharmacokinetics and bioavailability using an IV preparation and application of its use as a radiosensitizer. Cancer Treat Rep *64 (10–11):* 1087–1095

Raghuram TC, Krishnaswamy K 1981 Tetracycline absorption in malnutrition. Drug Nutr Interact *1:* 23–29

Rakhit A, Holford NHG, Guentert TW, Maloney K, Riegelman S 1984 Pharmacokinetics of quinidine and three of its metabolites in man. J Pharmacokinet Biopharm *12 (1):* 1–21

Rapeport WG 1985 Clinical pharmacokinetics of bretylium. Clin Pharmacokinet *10:* 248–256

Rattie ES, Bernardo PD, Ravin LJ 1976 Pharmacodynamic interpretation of cephradine levels in serum after intravenous and extravascular administration in humans. Antimicrob Agents Chemother *10 (2):* 283–287

Reece PA, Kotasek D, Morris RG, Dale BM, Sage RE 1986 The effect of food on oral melphalan absorption. Cancer Chemother Pharmacol *16 (2):* 194–197

Regardh CG, Jordo L, Ervik M, Lundborg P, Olsson R, Ronn O 1981 Pharmacokinetics of metoprolol in patients with hepatic cirrhosis. Clin Pharmacokinet *6:* 375–388

Reid JL, Meredith PA, Elliott HL 1983 Pharmacokinetics and pharmacodynamics of trimazosin in man. Am Heart J *106 (5):* 1222–1228

Resetarits DE, Bates TR 1979 Apparent dose-dependent absorption of chlorothiazide in dogs. J Pharmacokinet Biopharm *7 (5):* 463–470

Richards DA 1983 Comparative pharmacodynamics and pharmacokinetics of cimetidine and ranitidine. J Clin Gastroenterol *5 (Suppl 1):* 81–89

Rietbrock N, Guggenmos J, Kuhlmann J, Hess U 1976 Bioavailability and pharmacokinetics of beta-methyldigoxin after multiple oral and intravenous doses. Eur J Clin Pharmacol *9:* 373–379

Ritschel WA 1984 What is bioavailability? Philosophy of bioavailability testing. Meth Find Exptl Clin Pharmacol *12:* 777–786

Ritschel WA 1986 Handbook of basic pharmacokinetics. Hamilton, IL: Drug Intelligence Publiations Inc pp 142–167

Ritschel WA 1987 In vivo animal models for bioavailability assessment. S T P Pharma *3 (2):* 125–141

Ritschel WA 1987 a Methodology of bioavailability assessment. S T P Pharma *3 (4):* 286–301

Ritschel WA 1987 b Bioavailability: A Critical Evaluation. In: "Biotechnology in Health Care". Proc 37th Indian Pharm Congr New Delhi, Printorium Press, Ahmedabad, India pp 111–142

Ritschel WA, Hammer GV 1977 Pharmacokinetics of papaverine in man. Int J Clin Pharmacol Biopharm *15 (5):* 227–229

Ritschel WA, Brady ME, Tan HS 1979 First-pass effect of coumarin in man. Int J Clin Pharmacol Biopharm *17 (3):* 99–103

Riva E, Gerna M, Latini R, Giani P, Volpi A, Maggioni A 1982 Pharmacokinetics of amiodarone in man. J Cardiovasc Pharmacol *4 (2):* 264–269

Roberts CJC 1984 Clinical pharmacokinetics of ranitidine. Clin Pharmacokinet *9 (3):* 211–221

Robson RH, Prescott LF 1978 A pharmacodynamic study of doxapram in patients and volunteers. Br J Clin Pharmacol *7:* 81–87

Roholt K, Nielsen B, Kristensen E 1975 Pharmacodynamic studies with mecillinam and pivmecillinam. Chemotherapy *21:* 146–166

Rohss K, Andren K, Heggelund A, Lagerstrom PO, Lundborg P 1986 Bioavailability of omeprazole given in conjunction with food. Acta Pharmacol Toxicol *59 (Suppl 5):* 85

Rose JQ, Yurchak AM, Jusko WJ 1981 a Dose dependent pharmacokinetics of prednisone and prednisolone in man. J Pharmacokinet Biopharm *9 (4):* 389–417

Rose JQ, Yurchak AM, Meikle AW, Jusko WJ 1981 b Effect of smoking on prednisone, prednisolone, and dexamethasone pharmacokinetics. J Pharmacokinet Biopharm *9 (1):* 1–14

Ross-Lee LM, Eadie MJ, Hooper WD, Bochner F Single dose pharmacokinetics of metoclopramide. Eur J Clin Pharmacol *20 (6):* 465–471

Rowell FJ, Seymour RA, Rawlins MD 1983 Pharmacokinetics of intravenous and oral dihydrocodeine and its acid metabolites. Eur J Clin Pharmacol *25 (3):* 419–422

Rowland M, Riegelman S, Harris PA, Sholkoff SD 1972 Absorption kinetics of aspirin in man following oral administration of an aqueous solution. J Pharm Sci *61 (3):* 379–385

Rubin A, Rodda BE, Warrick P, Ridolfo AS, Gruber CM 1972 Physiological disposition of fenoprofen in man II: Plasma and urine pharmacokinetics after oral and intravenous administration. J Pharm Sci *61 (5):* 739–745

Rubin GM, Tozer TN 1984 Theoretical considerations in the calculation of bioavailability of drugs exhibiting Michaelis-Menten elimination kinetics. J Pharmacokinet Biopharm *12 (4):* 437–450

Rubin PC, Yee YG, Anderson M, Blaschke T 1979 Prazosin first-pass metabolism and hepatic extraction in the dog. J Cardiovasc Pharmacol *1 (6):* 641–647

Rubin PC, Scott PJ, Reid JL 1981 Prazosin disposition in young and elderly subjects. Br J Clin Pharmacol *12 (3):* 401–404

Runkel R, Chaplin M, Boost G, Segre E, Forchielli E 1972 a Absorption, distribution, metabolism, and excretion of naproxen in various laboratory animals and human subjects. J Pharm Sci *61 (5):* 703–708

Runkel RA, Kraft KS, Boost G, Sevelius H, Forchielli E, Hill R, Magoun R, Szakacs JB, Segre E 1972 b Naproxen oral absorption characteristics. Chem Pharm Bull *20 (7):* 1457–1466

Runkel R, Forchielli E, Boost G, Chaplin M, Hill R, Sevelius H, Thompson G, Segre E 1973 Naproxen metabolism, excretion, and comparative pharmacokinetics. Scand J Rheumatol *2 (Suppl):* 29–36

Rurak A, Melzacka M, Danek L 1981 Pharmacokinetics of trazodone after different routes of administration. Pol J Pharmacol Pharm *33 (3):* 341–348

Ryerfeldt A, Andersson P, Edsbacker S, Tonnesson M, Davies D, Pauwels R 1982 Pharmacokinetics and metabolism of budesonide, a selective glucocorticoid. Eur J Respir Dis *122 (Suppl):* 86–95

Safar ME, Chau NP, Levenson JA, Simon AC, Weiss YA 1978 Pharmacokinetics of intravenous and oral pindolol in hypertensive patients with chronic renal failure. Clin Sci Mol Med *55 (Suppl 4):* 275 S – 277 S

Said SA 1982 Pharmacokinetics and bioavailability of intravenous, intramuscular, and oral khellin in rats. Pharmazie *37 (5):* 384

Sakai K, Nishiura A, Fujihara Y, Kutsuna T, Nishino T 1983 Salivary excretion of warfarin in rabbits: Relationship between pharmacological effect and salivary pharmacokinetics of warfarin in rabbits. J Pharmacobiodyn *6 (12):* 991–999

Sams RA, Baggot JD 1977 Bioavailability, disposition kinetics, and dosage of sulfadimethoxine in dogs – a correction. Can J Comp Med *41 (4):* 479–480

Sasahara K, Nitanai T, Habara T, Morioka T, Nakajima E 1980 Dosage form design for the improvement of biovailability of levodopa II: Bioavailability of marketed levodopa preparations in dogs and parkinsonian patients. J Pharm Sci *69 (3):* 261–265

Sawe J 1986 High-dose morphine and methadone in cancer patients. Clinical pharmacodynamic considerations of oral treatment. Clin Pharmacokinet *11 (2):* 87–106

Schiantarelli P, Acerbi D, Bovis G 1981 Some pharmacokinetic properties and bioavailability of piroxicam administered orally or rectally to rodents and man. Arzneimittelforschung *31 (1):* 92–97

Schiavi M, Ventura P, Giachetti C, Poletti P, Canali S, Zanolo G 1987 Systemic availability of two oral trans-soberol formulations in healthy volunteers. Proc 3rd Eur Congr Biopharm Pharmacokinet Imp Reix Clermont-Ferrand p 109

Schneider H, Nightingale CH, Quintiliani R, Flanagan DR 1978 Evaluation of an oral prolonged-release antibiotic formulation. J Pharm Sci *67 (11):* 1620–1622

Schran HF, Tse FL, Bhuta SI 1985 Pharmacokinetics and pharmacodynamics of bromocriptine in the rat. Biopharm Drug Dispos *6 (3):* 301–311

Schulz P, Dick P, Blaschke TF, Hollister L 1985 Discrepancies between pharmacodynamic studies of amitriptyline. Clin Pharmacokinet *10:* 257–268

Segura J, Borja L, Bakke OM 1976 Pharmacokinetics of sulpiride after oral and intravenous administration in the rat and the dog. Arch Int Pharmacodyn Ther *223 (1):* 88–95

Selvig K 1981 Pharmacokinetics of proxyphylline in adults after intravenous and oral administration. Eur J Clin Pharmacol *19 (2):* 149–155

Shaffer JL, Kershaw A, Houston JB 1986 Disposition of metronidazole and its effects on sulphasalazine metabolism in patients with inflammatory bowel disease. Br J Clin Pharmacol *21 (4):* 431–435

Shann F, Stace J, Edstein M 1985 Pharmacokinetics of quinine in children. J Pediatr *106:* 506–510

Shibasaki J, Konishi R, Koike M, Imamura A, Sueyasu M 1981 Some quantitative evaluation of first-pass metabolism of salicylamide in rabbit and rat. J Pharmacobiodyn *4 (2):* 91–100

Shibasaki J, Konishi R, Takemura M, Fukushima E, Nakamura J, Sasaki H 1984 Comparison of the first-pass metabolism of ethenzamide and salicylamide in rats. J Pharmacobiodyn *7 (11):* 804–810

Siddoway LA, Woosley RL 1986 Clinical pharmacokinetics of disopyramide. Clin Pharmacokinet *11:* 214–222

Simon VC, Junk W, Malerczyk V 1976 Acidocillin: In vitro activity, pharmacokinetics, and therapeutic results in whooping cough. Arzneimittelforschung *26 (3):* 424–426

Singhvi SM, Kripalani KJ, Dean AV, Keim GR, Kulesza JS, Meeker FS, Ross JJ, Shaw JM, Migdalof BH 1981 Absorption and bioavailability of captopril in mice and rats after administration by gavage and in the diet. J Pharm Sci *70 (8):* 885–888

Sirtori CR, Franceschini G, Galli-Kienle M, Cighetti C, Galli G, Bondioli A, Conti F 1978 Disposition of metformin (N, N-dimethylbiguanide) in man. Clin Pharmacol Ther *24 (6):* 683–693

Smith DE, Lin ET, Benet LZ 1980 Absorption and disposition of furosemide in healthy volunteers, measured with a metabolite-specific assay. Drug Metab Dispos *8 (5):* 337–342

Smith MT, Heazlewood V, Eadie MJ, Brophy TOR, Tyrer JH 1984 Pharmacokinetics of midazolam in the aged. Eur J Clin Pharmacol *26:* 381–388

Smith RB, Kroboth PD, Vanderlugt JT, Phillips JP, Juhl RP 1984 Pharmacokinetics and pharmacodynamics of alprazolam after oral and IV administration. Psychopharmacology *84:* 452–456

Somogyi A, Gugler R 1983 Clinical pharmacokinetics of cimetidine. Clin Pharmacokinet *8 (6):* 463–495

Somogyi A, Rohner HG, Gugler R 1980 Pharmacokinetics and bioavailability of cimetidine in gastric and duodenal ulcer patients. Clin Pharmacokinet *5:* 84–94

Sorkin EM, Clissold SP 1987 Nicardipine. A review of its pharmacokinetic and pharmacodynamic properties, and therapeutic efficacy, in the treatment of angina pectoris, hypertension, and related cardiovascular disorders. Drugs *33 (4):* 296–345

Spino M, Chai RP, Isles AF, Thiessen JJ, Tesoro A, Gold R, MacLeod SM 1984 Cloxacillin absorption and disposition in cystic fibrosis. J Pediatr *105 (5):* 829–835

Spyker DA, Rugloski RJ, Vann RL, O'Brien WM 1977 Pharmacokinetics of amoxicillin: Dose dependence after intravenous, oral, and intramuscular administration. Antimicrob Agents Chemother *11 (1):* 132–141

Stella VJ, Chu CK 1980 Effect of short term exposure to polychlorinated biphenyls on first-pass metabolism of pentobarbital in rats. J Pharm Sci *69 (11):* 1279–1282

Stella VJ, Charman WNA, Naringreker VH 1985 Prodrugs. Do they have advantages in clinical practice? Drugs *29:* 455–473

Stenderup J, Eriksen J, Pedersen SB, Christiansen LV 1985 Pharmacokinetics of tolfenamic acid in patients with cirrhosis of the liver. Eur J Clin Pharmacol *28 (5):* 573–579

Steudel HC, Volkenandt M, Steudel AT 1983 Pharmacokinetics of isosorbide-5-mononitrate after oral and intravenous administration in patients with liver cirrhosis: First results. Z Kardiol *72 (Suppl 3):* 24–28

Stewart DJ, Nundy D, Maroun JA, Tetreault L, Prior J 1985 Bioavailability, pharmacokinetics, and clinical effects of an oral preparation of etoposide. Cancer Treat Rep *69 (3):* 269–273

Storstein L, Larsen A, Midtbo K, Soevareid L 1984 Pharmacokinetics of calcium blockers in patients with renal insufficiency and in geriatric patients. Acta Med Scand *681 (Suppl):* 25–30

Straehl P, Galeazzi RL 1985 Isosorbide dinitrate bioavailability, kinetics and metabolism. Clin Pharmacol Ther 38: 140–149

Straehl P, Galeazzi RL, Soliva M 1984 Isosorbide 5-mononitrate and isosorbide 2-mononitrate kinetics after intravenous and oral dosing. Clin Pharmacol Ther *36 (4):* 485–492

Straw JA, Szapary D, Wynn WT 1984 Pharmacokinetics of the diastereoisomers of leucovorin after intravenous and oral administration to normal subjects. Cancer Res *44 (7):* 3114–3119

Strong JM, Dutcher JS, Lee WK, Atkinson AJ 1975 Absolute bioavailability in man of N-acetylprocainamide determined by a novel stable isotope method. Clin Pharmacol Ther *18 (5):* 613–622

Stroshane RM, Koss RF, Biddlecome CE, Luczkowec C, Edelson J 1984 Oral and intravenous pharmacokinetics of milrinone in human volunteers. J Pharm Sci *73 (10):* 1438–1441

Sweatman TW, Renwick AG, Burgess CD 1981 The pharmacokinetics of saccharin in man. Xenobiotica *11 (8):* 531–540

Talbert RL, Bussey HI 1983 Update on calcium channel blocking agents. Clin Pharm *2:* 403–416

Talseth T 1976 Studies on hydralazine III. Bioavailability of hydralazine in man. Eur J Clin Pharmacol *10 (6):* 395–401

Tam YK, Axelson JE, McErlane B, Ongley R, Price JDE 1981 Dose dependent pharmacokinetics of metoclopramide in the rat: An effect of hemoperfusion? J Pharmacol Exp Ther *217 (3):* 764–769

Tanaka E, Kinoshita H, Yamamoto T, Kuroiwa Y, Takabatake E 1981 Pharmacodynamic studies of trimethadione and its metabolite in rats with chemical-induced liver injury. J Pharmacobiodyn *4 (8):* 576–583

Tanigawara Y, Yamaoka K, Nakagawa T, Uno T 1982 Moment analysis for the separation of mean in vivo disintegration, dissolution, absorption, and disposition time of ampicillin products. J Pharm Sci *71 (10):* 1129–1133

Tauber U, Haack D, Nieuweboer B, Kluss G, Vecsel P, Wendt H 1984 The pharmacokinetics of fluocortolone and prednisolone after intravenous and oral administration. Int J Clin Pharmacol Ther Toxicol *22 (1):* 48–55

Tauber U, Weiss C, Krause W, Acksteiner B, Matthes H 1985 Pharmacokinetics of pirazolac a new anti-inflammatory drug in human volunteers. Eur J Drug Metab Pharmacokinet *10 (1):* 41–53

Tauber U, Schroder K, Dusterberg B, Matthes H 1986 Absolute bioavailability of testosterone after oral administration of testosterone undecanoate and testosterone. Eur J Drug Metab Pharmacokinet *11 (2):* 145–149

Taylor G, Houston JB 1983 Determinants of systemic availability of promethazine in rabbits. J Pharm Pharmacol *35:* 284–288

Taylor G, Houston JB, Shaffer J, Mawer G 1983 Pharmacokinetics of promethazine and its sulphoxide metabolite after intravenous and oral administration to man. Br J Clin Pharmacol *15 (3):* 287–293

Taylor IW, Chausseaud LF, Waterworth G 1986 Pharmacokinetics of the novel anti-inflammatory agent ximoprofen in normal subjects and patients with renal disease and hepatic disease. Acta Pharmacol Toxicol *59 (Suppl 5):* 56

Taylor T, Chausseaud LF, Catanese B 1987 The pharmacokinetics of benzydamine in human subjects. Proc 3rd Eur Congr Biopharm Pharmacokinet Imp Reix Clermont-Ferrand p 273

Testa R, Airoldi L, Latini R 1978 Pharmacokinetics and bioavailability of alclofenac and its lysine-salt after different route of administration in the rabbit. Pharmacol Res Commun *10 (1):* 53–63

Thenot JP, Hermann P, Durand A, Burke J, Allen J, Vajta S, Albin H, Thebault JJ, Warrington SJ, Morselli PL 1987 Pharmacokinetics and metabolism of zolpidem in various animal species and in man. Proc 3rd Eur Congr Biopharm Pharmacokinet Imp Reix Clermont-Ferrand p 336

Thiercelin JF, Diquet B, Levesque C, Ghesquiere F, Simon P, Viars P 1984 Metronidazole kinetics and bioavailability in patients undergoing gastrointestinal surgery. Clin Pharmacol Ther *35 (4):* 510–519

Thiercelin JF, Dubruc C, Bianchetti G, Bercoff E, Bouchet JL, Emeriau JP, Lambert D, Vandel B, Thebault JJ 1987 Pharmacokinetics of zolpidem, a novel imidazopyridine hypnotic, in various physiopathological conditions. Proc 3rd Eur Congr Biopharm Pharmacokinet Imp Reix Clermont-Ferrand p 353

Timmer CJ, Pourbaix S, Desager JP, Sclavons M, Harvengt C 1985 Absolute bioavailability of mianserin tablets and solution in healthy humans. Eur J Drug Metab Pharmacokinet *10 (4):* 315–323

Titmarsh S, Monk JP 1987 Terazosin. A review of its pharmacokinetic and pharmacodynamic properties, and therapeutic efficacy in essential hypertension. Drugs *33 (5):* 461–477

Todd PA, Heel RC 1985 Suprofen. A review of its pharmacokinetic and pharmacodynamic properties, and analgesic efficacy. Drugs *30 (6):* 514–538

Trnovec T, Soltes L, Durisova M, Kallay Z, Koprda V, Piotrovskii LB 1985 Pharmacokinetics of ethimizol in man. Pharmazie *40 (6):* 410–411

Trouvin JH, Lepage S, Jacquot C 1987 Plasmatic and cerebral pharmacokinetics of tabernanthine in the rat: Influence of the route of administration. Proc 3rd Eur Congr Biopharm Pharmacokinet Imp Reix Clermont-Ferrand p 246

Tschammer T, Schudt C, Weinges KF, Zech K 1987 Pharmacokinetics of the new antimuscarinic drug telenzepine in healthy subjects by means of a radioreceptor assay. Proc 3rd Eur Congr Biopharm Pharmacokinet Imp Reix Clermont-Ferrand p 323

Tschopp JM, Gorgia A, Balant L, Revillard C, Francis RJ, Fabre J 1978 Role des metabolites dans les relations entre la pharmacocinetique et l'effet des agents beta-bloquants. Schweiz Med Wochenschr *108 (20):* 756–764

Tse FL, Welling PG 1977 Prednisolone bioavailability in the dog. J Pharm Sci *66 (12):* 1751–1754

Tse FL, Szeto DW 1982 Theophylline bioavailability in the dog. J Pharm Sci *71 (11):* 1301–1303

Tse FL, Sanders TM, Reo JP 1980 Bioavailability of propranalol in the dog. Arch Int Pharmacodyn Ther *248 (2):* 180–189

Ueda CT, Williamson BJ, Dzindzio BS 1976 Absolute quinidine bioavailability. Clin Pharmacol Ther *20 (3):* 260–265

Uribe M, Schalm WS, Summerskill WH, Go VL 1978 Oral prednisone for chronic active liver disease: Dose responses and bioavailability studies. Gut *19 (2):* 1131–1135

Urtasun RC, Rabin HR, Partington J 1983 Human pharmacokinetics and toxicity of high-dose metronidazole administered orally and intravenously. Surgery *93 (1):* 145–148

Vallner JJ, Steward JT, Kotzan JA, Kirsten EB, Honigberg IL 1981 Pharmacokinetics and bioavailability of hydromorphone following intravenous and oral administration to human subjects. J Clin Pharmacol *21 (4):* 152–156

Van Peer A, Woestenborghs R, Meuldermans W, Verlinden M, Heykants J, Reyntjens A 1987 Clinical pharmacokinetics of the gastrointestinal prokinetic drug cisapride. Proc 3rd Eur Congr Biopharm Pharmacokinet Imp Reix Clermont-Ferrand p 2311

Verbeeck RK, Branch RA, Wilkinson GR 1981 Meperidine disposition in man: Influence of urinary pH and route of administration. Clin Pharmacol Ther *30 (5):* 619–628

Verbeeck RK, Blackburn JL, Loewen GR 1983 Clinical pharmacokinetics of non-steroidal anti-inflammatory drugs. Clin Pharmacokinet *8:* 297–331

Vincent J, Elliott HL, Meredith PA, Reid JL 1985 a Trimazosin: Relationships between hypotensive effect, vascular responsiveness, and drug and metabolite concentrations. J Cardiovasc Pharmacol *7 (5):* 913–918

Vincent J, Meredith PA, Reid JL, Elliott HL, Rubin PC 1985 b Clinical pharmacokinetics of prazosin – 1985. Clin Pharmacokinet *10:* 144–154

Vincent J, Meredith PA, Elliott HL, Reid JL 1986 The pharmacokinetics of doxazosin in elderly normotensives. Br J Clin Pharmacol *21 (5):* 521–524

Vinge E, Arnold E, Rasmussen SN, Midskov C 1985 Single intravenous and oral doses of fenflumizole: Pharmacokinetics and effects on prostanoid formation. Acta Pharmacol Toxicol *57:* 121–129

Vogelgesang B, Echizen H, Schmidt E, Eichelbaum M 1984 Stereoselective first-pass metabolism of highly cleared drugs: Studies of the bioavailability of L- and D-verapamil examined with a stable isotope technique. Br J Clin Pharmacol *18:* 733–740

Vohringer HF, Wogenstein HM, Rietbrock N 1977 The biological availability of digitoxin. Fortschr Med *95 (38):* 2323–2325, 2328–2331

von Wittenau MS 1969 The oral absorption of doxycycline by man. Int J Clin Pharmacol Ther Toxicol *2 (1):* 52–55

Wagner JG 1972 An overview of the analysis and interpretation of bioavailability studies in man. Pharmacol *8:* 102–117

Wagner JG 1979 Fundamentals of clinical pharmacokinetics. Drug Intelligence Publications Inc, Hamilton, IL pp 337–358

Wagner T, Fenneberg K 1984 Pharmacokinetics and bioavailability of cyclophosphamide from oral formulations. Arzneimittelforschung *34 (3):* 313–316

Wahlin-Boll E, Almer LO, Melander A 1982 Bioavailability, pharmacokinetics, and effects of glipizide in type 2 diabetics. Clin Pharmacokinet *7 (4):* 363–372

Wall ME, Brine DR, Perez-Reyes M 1981 Metabolism and disposition of naltrexone in man after oral and intravenous administration. Drug Metab Dispos *9 (4):* 369–375

Wall ME, Sadler BM, Brine D, Taylor H, Perez-Reyes M 1983 Metabolism, disposition, and kinetics of delta-9-tetrahydrocannabinol in men and women. Clin Pharmacol Ther *34:* 352–363

Walle T 1985 Stereochemistry of the in vivo disposition and metabolism of propranolol in dog and man using deuterium-labeled pseudoracemates. Drug Metab Dispos *13 (3):* 279–282

Walle T, Fagan TC, Conradi EC, Walle UK, Gaffney TE 1979 Presystemic and systemic glucuronidation of propranolol. Clin Pharmacol Ther *26 (2):* 167–172

Waller DG, Renwick AG, Gruchy BS, George CF 1984 First-pass metabolism of nifedipine in man. Br J Clin Pharmacol *18:* 951–954

Walmsley LM 1984 Dose-dependent pharmacokinetics of clofibric acid in the non-human primate. Arch Toxicol *7 (Suppl):* 272–277

Wan SH, Koda RT, Maronde RF 1979 Pharmacokinetics, pharmacology of atenolol and effect of renal disease. Br J Clin Pharmacol *7 (6):* 569–574

Warrington SJ, Turner P, Kilborn JR, Bianchetti G, Morselli PL 1980 Blood concentrations and pharmacodynamic effects of betaxolol (SL-75212), a new beta-adrenoceptor antagonist after oral and intravenous administration. Br J Clin Pharmacol *10:* 449–452

Watari N, Funaki T, Aizawa K, Kaneniwa N 1983 Nonlinear assessment of nitrofurantoin bioavailability in rabbits. J Pharmacokinet Biopharm *11 (5):* 529–545

Weisner RH, Dickson ER, Carlson GL, McPhaul LW, Go VLW 1981 The pharmacokinetics of D-penicillamine in man. J Rheumatol *7 (Suppl):* 51–55

Wendt G 1982 Pharmacokinetics and metabolism of tiapamil. Cardiology *69 (Suppl 1):* 68–78

Whelpton R, Hurst P 1985 Bioavailability of oral physostigmine. N Engl J Med *313:* 1293–1294

White NJ 1985 Clinical pharmacokinetics of antimalarial drugs. Clin Pharmacokinet *10:* 187–215

Whiteman PD, Fowle ASE, Hamilton MJ, Peck AW, Bye A, Dean K, Webster A 1985 Pharmacokinetics and pharmacodynamics of procyclidine in man. Eur J Clin Pharmacol *28 (1):* 73–78

Wiesel FA, Alfredsson G, Ehrnebo M, Sedvall G 1980 The pharmacokinetics of intravenous and oral sulpiride in healthy human subjects. Eur J Clin Pharmacol *17 (5):* 385–391

Williams PE, Harding SM 1984 The absolute bioavailability of oral cefuroxime axetil in male and female volunteers after fasting and after food. J Antimicrob Chemother *13 (2):* 191

Willis JV, Kendall MJ, Jack DB 1980 A study of the effect of aspirin on the pharmacokinetics of oral and intravenous diclofenac sodium. Eur J Clin Pharmacol *18 (5):* 415–418

Wills RJ, Spiegel HE, Soike KF 1984 Pharmacokinetics of recombinant alpha A interferon following i. v. infusion and bolus, i. m., and p. o. administrations to African green monkeys. J Interferon Res *4 (3):* 399–409

Wilson TW, Firor WB, Johnson GE, Holmes GI, Tsianco MC, Huber PD, Davies RO 1982 Timolol and propranolol: Bioavailability, plasma concentrations, and beta blockade. Clin Pharmacol Ther *32:* 676–685

Witte PU, Irmisch R, Haidu P 1985 Pharmacokinetics of pheniramine (Avil) and metabolites in healthy subjects after oral and intravenous administration. Int J Clin Pharmacol Ther Toxicol *23 (1):* 59–62

Woodcock BG, Loh W, Habedank WD, Rietbrock N 1982 Dihydroergotoxine kinetics in healthy men after intravenous and oral administration. Clin Pharmacol Ther *32 (5):* 622

Woodhouse KW, Hamilton P, Lennard A, Rawlins MD 1983 The pharmacokinetics of melphalan in patients with multiple myeloma: An intravenous/oral study using a conventional dose regimen. Eur J Clin Pharmacol *24 (2):* 283–285

Woosley RL, Wang T, Stone W, Siddoway L, Thompson K, Duff HJ, Cerskus I, Roden D 1984 Pharmacology, electrophysiology, and pharmacokinetics of mexiletine. Am Heart J *107 (5):* 1058–1065

Workman P, White RAS, Talbot K 1986 CB-1954 revisited. Cancer Chemother Pharmacol *16 (1):* 1–8

Workman P, White RAS, Walton MI, Owen LN, Twentyman PR 1984 Preclinical pharmacokinetics of benznidazole. Br J Cancer *50:* 291–303

Workman RJ, Vaughn WK, Stone WJ 1986 Dexamethasone suppression testing in chronic renal failure: Pharmacokinetics of dexamethasone and demonstration of a normal hypothalamic-pituitary-adrenal axis. J Clin Endocrinol Metab *63 (3):* 741–746

Wright GJ, Pitts JE 1984 Bioavailability of metoclopramide from tablet and liquid dosage forms relative to intravenous injection. Clin Pharmacol Ther *35 (2):* 284

Wright WE, Wheeler WJ, Line VD, Frogge JA, Finley DR 1979 Orally active esters of cephalosporin antibiotics II. Synthesis and biological properties of the acetoxymethyl ester of cefamandole. J Antibiot *32 (11):* 1155–1160

Yacobi A, Kamath BL, Stampfli HF, Look ZM, Lai CM 1983 Age-related pharmacokinetics of N-acetylprocainamide in rats. J Pharm Sci *72 (7):* 789–792

Yeh KC 1985 Pharmacodynamic overview of indomethacin and sustained release indomethacin. Am J Med *79 (Suppl 42):* 3–12

Yokohama S, Yamashita K, Toguchi H, Takeuchi J, Kitamori N 1984 a Absorption of thyrotropin-releasing hormone after oral administration of TRH tartrate monohydrate in the rat, dog, and human. J Pharmacobiodyn *7 (2):* 101–111

Yokohama S, Yoshioka T, Kitamori N 1984 b Absorption of gammabutyrolactone-gamma-carbonyl-L-histidyl-L-prolinamide citrate (DN-1417), an analog of thyrotropin-releasing hormone, in rats and dogs. J Pharmacobiodyn *7 (8):* 527–535

Yoshimura M, Kojima J, Ito T, Fujii M, Suzuki J 1985 Pharmacokinetics od nipradilol (K-351), a new antihypertensive agent. II. Influence of the route of administration on bioavailability in dogs. J Pharmacobiodyn *8 (7):* 503–512

Yue TL, Varma DR 1982 Pharmacokinetics, metabolism and disposition of salicylate in protein-deficient rats. Drug Metab Dispos *10 (2):* 147–152

Zech K, Herzog R, Maier A, David M 1987 Pharmacokinetics of the new long acting calcium antagonist B 859–34 (+ enantiomer) in comparison with its racemate in dogs. Proc 3rd Eur Congr Biopharm Pharmacokinet Imp Reix Clermond-Ferrand p 214

Zimm S, Collins JM, O'Neil D, Chabner BA, Poplack DG 1983 Inhibition of first-pass metabolism in cancer chemotherapy: Interaction of 6-mercaptopurine and allopurinol. Clin Pharmacol Ther *34 (6):* 810–817

Zuidema J, Verhoeven J, Merkus FWH 1981 Pharmacokinetics of etofylline after intravenous and oral administration to humans. Int J Clin Pharmacol Ther Toxicol *19:* 310–313

Zulliger HW, Fassolt A 1985 Pharmacokinetics and bioavailability of suprofen injection solution after intravenous application versus capsules on six healthy male volunteers. Arzneimittelforschung *35 (6):* 976–980