

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.

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:

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

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:

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

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 determination 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:

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

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:

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

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 amount 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], particularly 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, cephalixin, diflusal, 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
Acidocillin				74	Pedersen and FitzGerald 1984
Acyclovir		80–90		15–50	Simon et al. 1976
Alclofenac	88 ^c			36–96	Krasny et al. 1981, Laskin 1983, Peterslund et al. 1984
Alizapride				75–93	Testa et al. 1978, Verbeeck et al. 1983
Allopurinol				90±9	Houin et al. 1984
Alprazolam				88	Breithaupt and Tittel 1982, Murell and Rapeport 1986
Alprenolol				9±6	Smith et al. 1984
Amantadine				95±5	Johnsson and Regardh 1976
Amiodarone				22–86	Benet et al. 1984
Amitriptyline				46±9	Latini et al. 1984, Pourbaix et al. 1985, Riva et al. 1982
Amlodipine				52–88	Pond and Tozer 1984, Schulz et al. 1985
Amosulalol				100	Faulkner et al. 1986
Amoxicillin				93±10	Nakashima et al. 1984
Amphotericin B				<10	Arancibia et al. 1980, Spyker et al. 1977
Ampicillin				62±17	Benet et al. 1984
Amrinone				93±12	Ehrnebo et al. 1979, Tanigawara et al. 1982
Amsacrine	90±10 ^c				Park et al. 1983
Aprinidine				85–95	Paxton 1986
Atenolol				54±12	Benet et al. 1984
Azosemide				10	Fitzgerald et al. 1978, Johnsson and Regardh 1976, Mason et al. 1979
Benzidamine				59–128	Meier 1982, Wan et al. 1979
Benznidazole		130			Brater et al. 1983
Bepidil				60	Taylor et al. 1987
Betaxolol				90	Workman et al. 1984
Biperiden				33±5	Benet 1985
Bretylium				12–37	Warrington et al. 1980
Bromocriptine	6 ^a				Grimaldi et al. 1986
Bromopride				49	Garrett et al. 1982, Rapeport 1985
Brotizolam				70±22	Schran et al. 1985
Budesonide				11±4	Brodie et al. 1986
Bufloxedil				50–80	Jochemsen et al. 1983 a and b
Bufuralol				46±15	Ryerfeldt et al. 1982
Bumetanide				66±11	Clissold et al. 1987
Bupropion				60–80	Dayer et al. 1982, Tschopp et al. 1978
Buspirone				3	Holazo et al. 1984, Lau et al. 1986
Butylmorphine	10 ^a				Benet et al. 1984
					Gammans et al. 1986
					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 et 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
Diffunisal				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
Ethinylestradiol	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 ^b	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. 1982 a 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
Methyl digoxin				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 Kretschmar 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. 1983b, 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
Probucof	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
Propoxyphenen				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
Proxiphylline				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-Bechant 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 ^c	67±4	Thenot et al. 1987, Thiercelin et al. 1987
Zopiclone				80	Goa and Heel 1986

^arats, ^brhesus monkeys, ^crabbits, ^dmice, ^ecynomolgus monkeys, ^fbaboons, ^gafrican green monkeys, ^hsimilar results obtained in minipigs, ⁱsimilar results obtained in horses.

Table 2. Percent absolute oral bioavailability of prodrugs. Absolute oral bioavailability 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. 1983 a
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. 1981 a and b
Pivaloyloxyethyl Methyl dopa	Methyl dopa		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

^adogs, ^brhesus monkeys, ^cmice

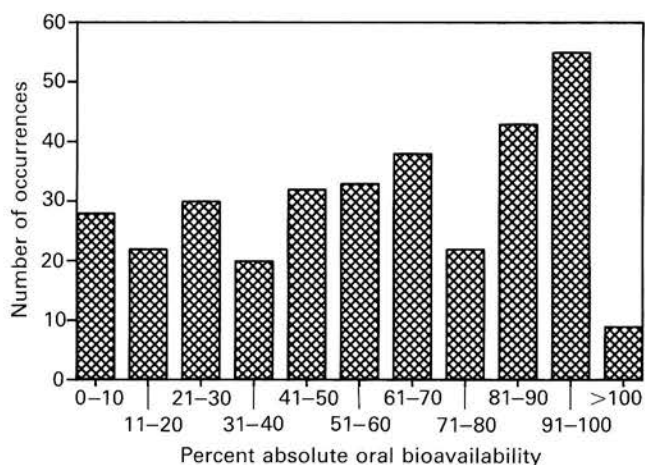


Fig. 1. The absolute oral bioavailability of selected drugs in man. The data shown are derived from Table 1.

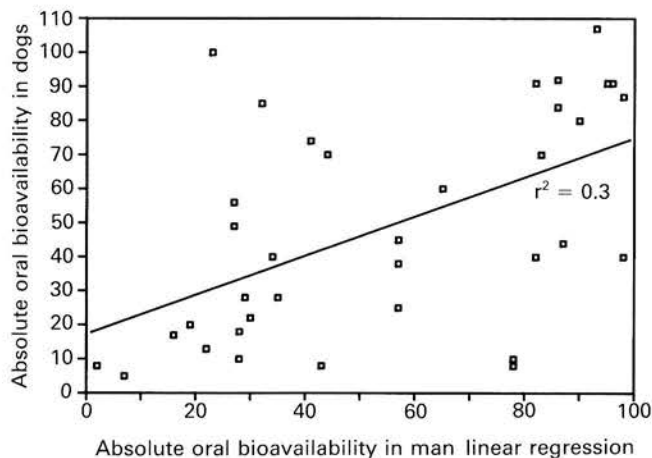


Fig. 3. A comparison of the absolute oral bioavailability of selected drugs in dogs and humans. The data shown are derived from Table 1.

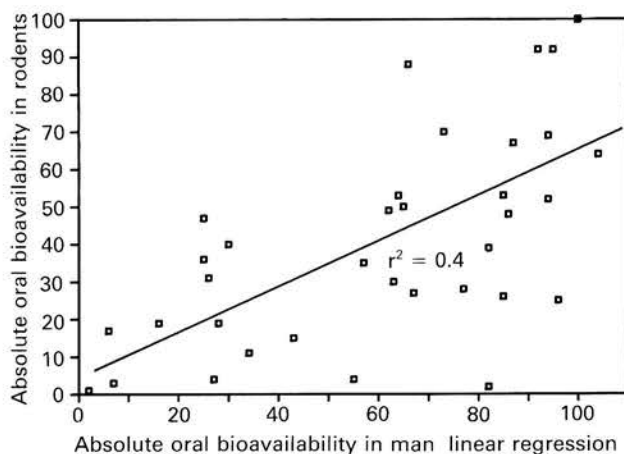


Fig. 2. A comparison of the absolute oral bioavailability of selected drugs in rodents and humans. The data shown are derived from Table 1.

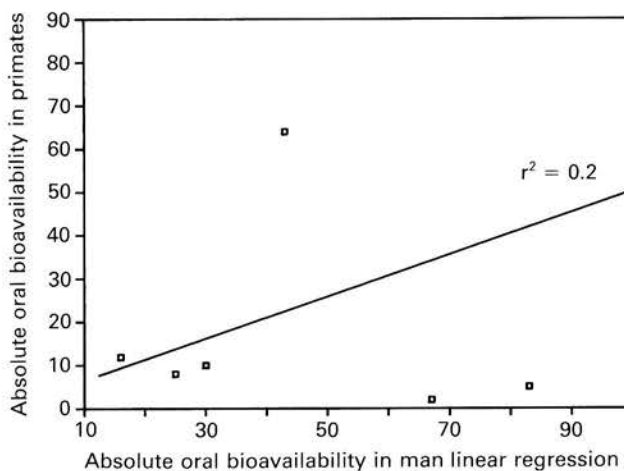


Fig. 4. A comparison of the absolute oral bioavailability of selected drugs in primates and humans. The data shown are derived from Table 1.

which bioavailability 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, methotrimiprazine, 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 important 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, particularly 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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