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COMMENTARIES

Interpatient variability in bioavailability is related to the extent of absorption: Implications for bioavailability and bioequivalence studies

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Bioavailability, by definition, involves the rate and extent to which a drug is absorbed into the systemic circulation.[1,2] The concept of bioavailability was first established during the early 1960s and was based on the observation that an active drug when administered in the same dose, but formulated in either comparable or different drug products, oftentimes differed therapeutically. These findings led to the establishment of specific regulatory guidelines by the U.S. Food and Drug Administration (FDA), and by 1970 the FDA required the characterization of biological availability for all new drugs intended for oral use. In more recent years, with the passage of the Drug Price Competition and Patent Restoration Act, the FDA began to require that all manufacturers of generic drugs demonstrate bioequivalence between their product and that of the innovator.

Since that time, a significant number of developments have been made in the areas of bioavailability and bioequivalence testing by regulatory agencies, academia, and the pharmaceutical industry. However, in spite of these accomplishments a number of unresolved issues relating to study design and data analysis methods still exist.[3-5] One topic in particular that has recently received a great deal of attention is subject variability. To date, most reports have focused primarily on the problem of intrasubject variability in bioavailability,[6-9] whereas little emphasis has been placed on intersubject variability. Consequently, no information is currently available with respect to the relationship between intersubject variability and bioavailability. Therefore the pur-

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pose of the this article is to examine the relationship between absolute bioavailability and the intersubject variability in bioavailability. The hypothesis to be tested is that the lower a drug's bioavailability is, the greater the intersubject variability in bioavailability. If this hypothesis is found to be true, such a relationship, in addition to being an important clinical pharmacologic principle, could have an impact on how bioavailability and bioequivalence studies are designed and interpreted.

METHODS

To address this issue, we decided to focus on publications reporting oral bioavailability results in one clinical pharmacology journal, namely, *Clinical Pharmacology & Therapeutics.* If this initial investigation were positive, subsequent research could involve a more complete examination of the literature.

Data collection. All issues of *Clinical Pharmacology & Therapeutics* over a 25-year period, or from January 1970 through December 1994, were examined. Articles that reported oral bioavailability data were collected and screened. The criteria used for the initial screening of journal articles were as follows: (1) the mean absolute bioavailability, or sufficient data to calculate the mean absolute bioavailability of an oral dosage form (i.e., tablet, capsule, or solution), was provided; (2) the intersubject variability in bioavailability, or sufficient data to calculate the intersubject variability in bioavailability, of an oral dosage form was provided; (3) the sample size *(n)* was provided; (4) the study was conducted in normal volunteers or in patients with normal kidney and liver function; and (5) the absolute bioavailability was calculated from the area under the plasma, serum, or blood drug concentration versus time curve (AUC) and not from urinary excretion data. Once it was determined that each study met the above requirements, the following information was recorded for further analysis: the type of subjects (i.e., healthy volunteers or patients), the gender and ages of the subjects, the type of assay method used to quantitate drug concentrations (i.e., chromatographic or immunologic), the number of half-lives over which drug concentrations were determined, the type of oral dosage form administered (i.e., tablet, capsule, or solution), the measure of variability of bioavailability reported (i.e., standard deviation [SD], standard error of the mean [SEM], or coefficient of variation [CV]), the study design implemented (i.e., randomized crossover, crossover-like but with only a single sequence, and/or without mention of randomization), the mean bioavailability *(F),* its variability, and the sample size. If needed, the variability was calculated from data given in the article. All data were subsequently tabulated, and bioavailability versus intersubject variability plots were prepared for statistical analyses.

Statistical analysis. In this article we use the term "intersubject variability" to refer to the total intersubject variability. The total intersubject variability includes the intrasubject variability and a "pure" intersubject component of variability. The relationship between estimated intersubject coefficient of variation and estimated bioavailability was assessed by regression analysis without weighting for sample size. We report Pearson correlation coefficients *(r)* and show the slopes from the linear regressions of coefficient of variation on bioavailability on the plots.

RESULTS

In this investigation, 143 papers were identified that reported absolute oral bioavailability data for 100 drugs that satisfied the search criteria (see Appendix I for a listing of the specific drugs and contributing references). In these articles, absolute oral bioavailability estimates ranged from 0.88% to 122%, with a mean bioavailability of 55.1%. The number of subjects per study ranged from three to 58, with a mean of 7.80. The relative frequencies of occurrence of several subject and study characteristics among these articles are summarized in Table I. Frequency ratios and percentages for all variables are based on a total of 143 references, with the exception of formulation type, which is based on a total of 149. The reason for this difference is that six studies reported absolute bioavailability estimates for two different oral formulations.

Subject characteristics. As shown in Table I, the vast majority of the studies were conducted in normal volunteers (80.4%), whereas a substantially smaller proportion were carried out in a patient population (17.5%). Even fewer investigations were conducted with normal volunteers and patients together in the same study (2.1%). A similar disparity was evident with respect to the gender of the subjects used, with 51.0% of the studies being conducted in men only and just 3.5% being conducted in women only. A subject population composed of both males and females was used in 35.7% of the investigations. In most studies, the age of the subjects ranged from 20 to 60 years of age (67.1%), whereas only 0.7% were

Table I. Relative frequencies of occurrence of various subject and study characteristics among 143 references reporting absolute oral bioavailability data in *Clinical Pharmacology & Therapeutics* between 1970 and 1994

Parameter	*Frequency*	*Percentage*
Subjects		
Not reported	0/143	0.0
Healthy volunteers	115/143	80.4
Patients	25/143	17.5
Mixed	3/143	2.1
Gender		
Not reported	14/143	9.8
Male	73/143	51.0
Female	5/143	3.5
Mixed	51/143	35.7
Age (yr)		
Not reported	9/143	6.3
<20	0/143	0.0
20-60	96/143	67.1
>60	1/143	0.7
Mixed	37/143	25.9
Assay method		
Not reported	1/143	0.7
Chromatographic	107/143	74.8
Immunologic	19/143	13.3
Other	16/143	11.2
Sampling (no. of half-lives)		
Not reported	3/143	2.1
>2 (but <3)	32/143	22.4
>3 (but <4)	33/143	23.1
>4 (but <5)	24/143	16.8
>5	41/143	35.6
Formulation		
Not reported	41/149	27.5
Tablet	53/149	35.6
Capsule	24/149	16.1
Solution	31/149	20.8
Variability reported		
Not reported	16/143	11.2
SD	83/143	58.0
SEM	39/143	27.3
CV	5/143	3.5
Study design		
Not reported		
1970-1978	14/34	41.2
1979-1987	22/85	25.9
1988-1994	4/24	16.7
Crossover		
1970-1978	11/34	32.4
1979-1987	26/85	30.6
1988-1994	6/24	25.0
Randomized crossover		
1970-1978	9/34	26.4
1979-1987	37/85	43.5
1988-1994	14/24	58.3

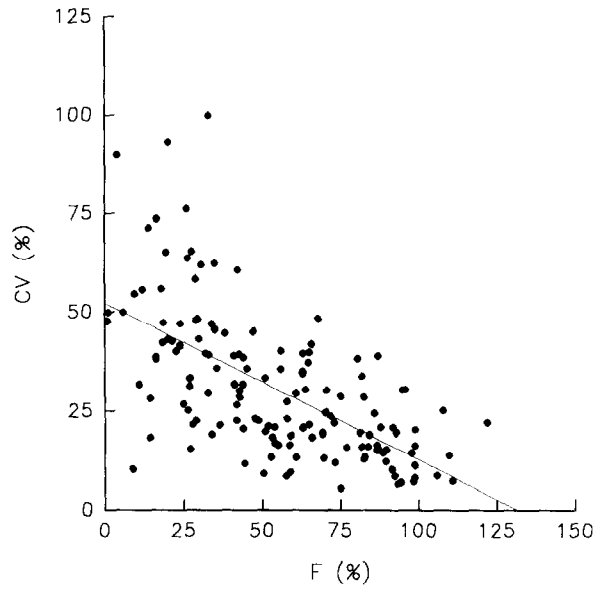

Fig. 1. Relationship between absolute bioavailability *(F)* and intersubject variability (CV) in absolute bioavailability for all studies evaluated (n = 149). Data were obtained from a total of 143 references reporting absolute oral bioavailability data in *Clinical Pharmacology & Therapeutics* between 1970 and 1994. The total number of drugs studied was 100, the majority of which were cardiovascular system agents (38), central nervous system agents (25), and antiinfective agents (9).

carried out with subjects older than 60. None of the studies determined oral bioavailability exclu sively in subjects below the age of 20. However, several studies (25.9%) were conducted with a combination of subjects from all three age groups.

Relationships between bioavailability and variability. Fig. 1 illustrates the relationship between absolute bioavailability *(F)* and intersubject variability (CV) in absolute bioavailability for all 149 data points. Regression analysis of the data revealed a significant inverse linear relationship between the two variables of interest ($p < 0.001$; $r = 0.624$). This finding is consistent with our hypothesis that the lower a drug's bioavailability, the greater the intersubject variability in bioavailability, and the higher a drug's bioavailability, the smaller the intersubject variability in this parameter.

The relationship between absolute bioavailability *(F)* and intersubject variability (CV) in absolute bioavailability by type of subjects is shown in Fig. 2. When the data were stratified according to subject type, regression analysis demonstrated an inverse linear relationship between the two variables of in-

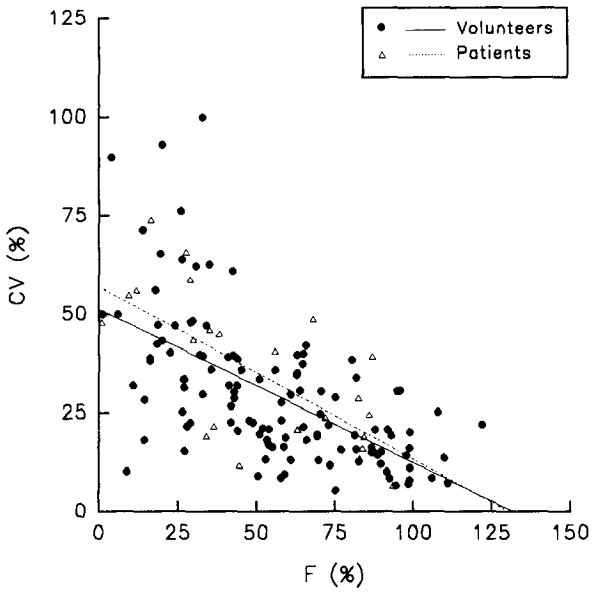

Fig. 2. Relationship between absolute bioavailability *(F)* and intersubject variability (CV) in absolute bioavailability by type of subjects (n = 146). See *legend* of Fig. 1 for source of data.

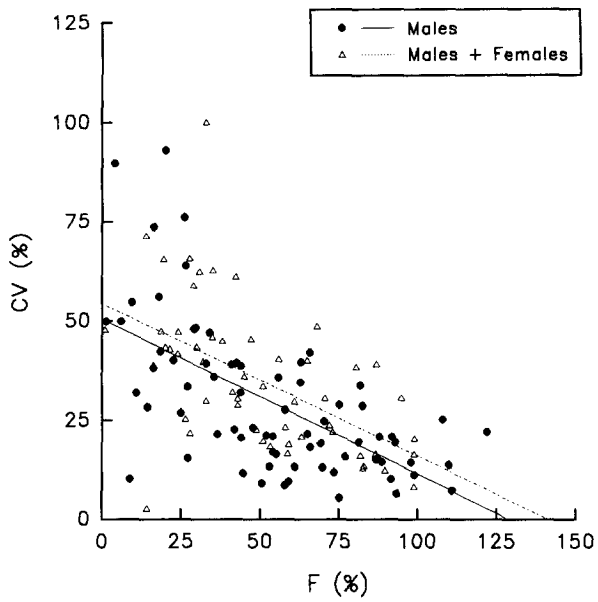

Fig. 3. Relationship between absolute bioavailability *(F)* and intersubject variability (CV) in absolute bioavailability by gender (n = 129). See *legend* of Fig. 1 for source of data.

terest for both healthy volunteers ($p < 0.001$; r = 0.614) and patients ($p < 0.001$; r = 0.674).

Fig. 3 shows the relationship between absolute bioavailability *(F)* and intersubject variability (CV) in absolute bioavailability by gender. Because few investigations were conducted with female subjects (3.5%), a direct comparison between men and women was precluded. Therefore an analysis was done to compare studies conducted solely in male subjects with those conducted in a subject population made up of both genders. Regression analysis showed a significant relationship between bioavailability and interpatient variability in bioavailability for studies conducted in male subjects ($p < 0.001$; r = 0.625), as well as for those conducted in a subject population comprised of both men and women ($p < 0.001$; r = 0.541).

DISCUSSION

Over the past several decades, bioavailability and bioequivalence studies have become an important part of drug development. As a result, much interest has focused on the science of bioavailability and bioequivalence testing. One area in particular that has recently received a great deal of interest is that of subject variability.[6-9] In this investigation, we examined the relationship between absolute oral bioavailability and the variability in this parameter. Our results clearly show a significant relationship between the absolute bioavailability of an oral dosage form and its intersubject coefficient of variation. Specifically, we observed an inverse association between the absolute bioavailability of a drug and the total variability in absolute bioavailability.

The total intersubject variability of bioavailability, as reported here, has both intrasubject and intersubject components. The design of absolute bioavailability studies does not permit separate estimation of these two components of variability. We can only speculate that each component follows the same inverse association as found here for the total variability. In contrast, bioequivalence studies yield estimates of the intrasubject variability (see Steinjans et al.[9] for a tabulation of some of these variabilities).

These findings have a number of important implications. First, because most bioequivalence (comparative bioavailability) studies today are conducted with a randomized crossover design with a single panel of subjects, only the intrasubject component of variability contributes to the error in determining relative bioavailability. If the relationship we have observed here also applies to the intrasubject component of variability, low bioavailability products will require larger studies (more subjects).

Second, there are important clinical implications. Because the intersubject component of variability is almost always larger than the intrasubject component, we can be reasonably confident that the results we have reported here do apply to the intersubject component. The consequence is that low bioavailability products will show more patient-to-patient variability than more bioavailable products. Therefore it is important that care be taken when prescribing low bioavailability drugs; these are the products for which the results of the bioavailability studies and even previous clinical experience are less likely to apply to a new patient. This is especially true when considering low bioavailability drugs with a narrow "therapeutic window" for which there is an increased risk of toxicity.

Another potential clinical implication concerns regulatory criteria for bioequivalence. Current criteria in the United States, Canada, and Europe require only evidence of equivalence in average bioavailability of generic drug products to the innovator product. It is conceivable that two drug products that are similar in average bioavailability may differ in variability of bioavailability. This would seem to be of particular potential for products with low bioavailability (and hence often with high variability). To address this problem, it has been suggested that, in addition to establishing bioequivalence in average bioavailability, bioequivalence in variability should also be confirmed.[10-12]

An interesting finding in the study was that the relationship between absolute bioavailability and intersubject variability in bioavailability was not influenced by subject type or gender. In recent years, the issue of gender-related differences in bioavailability has received much attention and, until recently, women were typically excluded from bioavailability and bioequivalence trials. One of the primary reasons for the exclusion of women was the belief that hormonal fluctuation during different phases of the menstrual cycle may increase variability. However, a recent review of the literature by the FDA revealed little evidence for an effect of menstrual cycle on the variability of pharmacokinetic parameters of drugs.[13] Similar findings were reported by Chen and Williams,[5] who observed no difference between men and women in within-subject variability for AUC and peak plasma drug concentration after oral administration (C_{max}). The relationship between absolute bioavailability and the intersubject variability in bioavailability according to subject type has been less well studied. However, based on the data from the present investigation, it appears that the extent of variability in this parameter is independent of the type of subjects used. More detailed studies will be necessary to determine if such differences do in fact exist.

Clearly, variability is important. In conducting this review, we found that many authors (11%) did not recognize this importance: their articles did not report the variability of the product, although it could be calculated from the data provided. Of those articles that did report variability, many (27% of all articles) reported the standard error of the mean. The standard error is a measure of the precision with which the average bioavailability is estimated and depends, in part, on the sample size of the study. The variability of the bioavailability of the product is estimated by the standard deviation or the coefficient of variation, and we recommend that reporting of either be the standard.

Finally, we want to add that this review highlights the improvement in the conduct in absolute bioavailability studies during the years covered by this review. In the later years, the majority of studies were designed as randomized crossover studies. In earlier years, randomization was much rarer; often, the article did not mention design at all. Because it is generally assumed that randomized crossover designs are superior, one may expect less variability to result in the estimation of bioavailability from these types of studies compared with those that implement a crossover-like design but with only a single sequence of drug administration. However, it is interesting to note that when these two types of study designs were compared with use of data from the present analysis, little difference was observed between them with respect to their relationships between bioavailability and coefficient of variation (data not shown).

In summary, the results of this investigation clearly show a significant inverse linear relationship between the bioavailability of a drug and its coefficient of variation. Moreover, similar relationships were observed when the data was stratified according to subject type and gender. These findings, in addition to being of clinical significance, could have an impact on how bioavailability and bioequivalence studies are designed and interpreted.

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APPENDIX I

List of drugs and contributing references used in the present analysis. All references were published in *Clinical Pharmacology & Therapeutics* between 1970 and 1994.

Cardiovascular system agents

Acebutolol: Meffin PJ et al. 1978;24:542-7.

N-Acetylprocainamide: Strong JM et al. 1975;18:613-22; Atkinson AJ et al. 1989;46:182-9.

Amiodarone: Pourbaix S et al. 1985;37:118-23.

Amlodipine: Abernethy DR et al. 1990;48:76-86.

Amosulalol: Nakashima M et al. 1984;36:436-43.

Atenolol: Mason WD et al. 1979;25:408-15.

Bidisomide: Page RL et al. 1992;51:371-8.

Bretylium tosylate (bretylium tosilate): Anderson JL et al. 1980;28:468-78.

Clonidine: Davies DS et al. 1976;21:593-601.

Digoxin: Huffman DH et al. 1974;16:310-7; Marcus FI et al. 1976;20:253-9; Cusack B et al. 1979;25:772-6; Hager WD et al. 1981;30:594-9.

Dilevalol: Tenero DM et al. 1989;46:648-56.

Dipyridamole: Mahony C et al. 1982;31:330-8.

Encainide: Bergstrand RH et al. 1986;40:148-54.

Felodipine: Edgar B et al. 1985; 38:205-11.

Fenoximone: Alken RG et al. 1984;36:209-16.

Hydralazine: Shepherd AMM et al. 1980;28:804-11; Reece PA et al. 1980;28:769-78; Crawford MH et al. 1985;38:538-43.

Isosorbide dinitrate: Straehl P, Galeazzi RL 1985;38:140-9.

Isosorbide 5-mononitrate: Major RM et al. 1984;35:653-59.

Labetalol: Lalonde RL et al. 1990;48:509-19.

Lidocaine: Boyes RN et al. 1970;12:105-6; deBoer AG et al. 1979;26:701-9; Huet PM, Lelorier J 1980;28:208-15.

Medroxalol: Hacgelc KD et al. 1983;3:785-91.

Metoprolol: Hogstedt S et al. 1985;37:688-92.

Mexiletine: Haselbarth V et al. 1981;29:729-36.

Nicainoprol: Ishizaki T et al. 1987;42:525-34.

Nifedipine: Kleinbloesem CH et al. 1985;37:563-74; Kleinbloesem CH et al. 1986;40:21-8.

Nisoldipine: van Harten J et al. 1988;43:332-41.

Oxprenolol: Mason WD, Winer N 1976;20:401-12.

Pamatolol: Carruthers SG et al. 1979;26:682-5.

Pindolol: Chau N et al. 1977;22:505-10.

Pirmenol: Hammill SC et al. 1982;32:686-91.

Prazosin: Chau N et al. 1980;28:6-11; Grahnen A et al. 1981;30:439-46.

Procainamide: Graffner C et al. 1974;17:414-23.

Propafenone: Haefeli EW et al. 1990;48:245-54.

Propranolol: Vestal RE et al. 1979;25:19-24; Jackman GP et al. 1981;30:291-6; Wilson TW et al. 1982;32:676-85; Wells PG et al. 1983;33:603-8; Olanoff LS et al. 1986;40:408-14.

Quinidine: Ueda CT et al. 1976;20:260-5.

Timolol: Wilson TW et al. 1982;32:676-85.

Tocainide: Lalka D et al. 1976;19:757-66.

Verapamil: Freedman SB et al. 1981;30:644-52; Kates RE et al. 1981;30:44-51; McAllister RG, Kirsten EB 1982;31:418-26; Smith MS et al. 1984;36:551-4; Abernethy DH et al. 1985;38:342-9.

Central nervous system agents

Amitriptyline: Schulz P et al. 1983;33:360-6.

Amobarbital: Inaba T et al. 1976;20:439-44.

Caffeine: Cheng WSC et al. 1990;47:516-24.

Codeine: Guay DRP et al. 1988;43:63-71.

Haloperidol: Holley FO et al. 1983;33:477-84.

Imipramine: Gram LF, Christiansen J 1975;17:555-63; Abernethy DR et al. 1984;35:792-97; Ciraulo DA et al. 1988;43:509-18.

Lorazepam: Greenblatt DJ et al. 1979;26:103-13; Morrison G et al. 1984;35:646-52; Herman RJ et al. 1989;46:18-25.

Lormetazepam: Humpel M et al. 1980;28673-9.

Meperidine (pethidine): Verbeeck RK et al. 1981;30:619-28; Pond SM et al. 1981;30:83-8; Pond SM, Kretschzmar KM 1981;30:680-6;Herman RJ et al. 1985;37:19-24.

Midazolam: Allonen H et al. 1981;30:653-61; Klotz U, Ziegler G 1982;32:107-12; Fee JPH et al. 1987;41:80-4; Mandema JW et al. 1992;51:715-28; Olkkola KT et al. 1993;53:298-305.

Moclobemide: Schoerlin MP et al. 1987;42:395-404; Schoerlin MP et al. 1991;49:32-8.

Morphine: Sawe J et al. 1981;30:629-35; Osborne R et al. 1990;47:12-9.

Nalbuphine: Jaillon P et al. 1989;46:226-33.

Nicotine: Benowitz NL et al. 1991;49:270-7.

Nortriptyline: Gram LF, Fredricson Overo K. 1975;188: 305-14.

Nomifensine: Lindberg RL et al. 1986;39:384-8.

Oxycodone: Leow KP et al. 1992;52:487-95.

Pentazocine: Ehrnebo M et al. 1977;22:888-92.

Phenytoin: Gugler R et al. 1975;19:135-42; Jung D et al. 1980;28:479-85; Sandor P et al. 1981;30:390-7.

Pyridostigmine: Breyer-Pfaff U et al. 1985;37:495-501.

Risperidone: Huang ML et al. 1993;54:257-68.

Tetrahydrocannabinol (THC): Ohlsson A et al. 1980;28: 409-16.

Trazodone: Greenblatt DJ et al. 1987;42:193-200.

Trimipramine: Abernethy DR et al. 1984;35:348-53.

Valproate: Klotz U, Antonin KH 1977;21:736-43.

Urinary tract system agents

Bumetanide: Lau HSH et al. 1986;39:635-45; Cook JA et al. 1988;44:487-500.

Furosemide: Kelly MR et al. 1973;15:178-86; Rane A et al. 1978;24:199-207; Villeneuve JP et al. 1986;40:14-20.

Antiinfectives

Amoxicillin (amoxicilline): Zarowny D et al. 1974;16: 1045-51.

3'-Azido-3'-deoxythymidine: Klecker RW et al. 1987;41: 407-12.

Cloxacillin: Nauta EH, Mattie H 1976;20:98-108.

Dicloxacillin: Nauta EH, Mattie H 1976;20:98-108.

Didanosine: Knupp CA et al. 1991;49:523-35.

Flucytosine: Cutler RE et al. 1978;24:333-42.

Metronidazole: Jensen JC, Gugler R 1983;34:481-7.

Nitrofurantoin: Hoener BA, Patterson SE 1981;29:808-16.

Ribavirin: Lertora JJL et al. 1991;50:442-9.

Hepatogastroenterologic agents

Cimetidine: Sonne J et al. 1981;29:191-7.

Nizatidine: Knadler MP et al. 1987;42:514-20; Aronoff GR et al. 1988;43:688-95.

Oxmetidine: Gugler R et al. 1982;31:501-8.

Ranitidine: Chau N et al. 1982;31:770-4; Garg DC et al. 1983;33:445-52.

Antineoplastic and immunomodulating agents

Cyclosporine (ciclosporin): Ptachcinski RJ et al. 1985;38: 296-300; Frey FJ et al. 1988;43:55-62; Hebert MF et al. 1992;52:453-7; Tan KKC et al. 1993;53:544-54.

Difluoromethylornithine: Haegele KD et al. 1981;30: 210-7.

6-Mercaptopurine: Zimm S et al. 1983;34:810-7.

Methotrexate: Stewart CF et al. 1990;47:540-6.

Endocrine and metabolism agents

Dexamethasone: Duggan DE et al. 1975;18:205-9.

Flunisolide: Chaplin MD et al. 1980;27:402-13.

Methylprednisolone: Derendorf H et al. 1985;37:502-7.

Norethindrone (norethisterone): Back DJ et al. 1978;24: 448-53.

Prednisolone: Petereit LB, Meikle AW 1977;22:912-6; Tanner A et al. 1979;25:571-8.

Respiratory system and antiallergy agents

Diphenhydramine: Spector R et al. 1980;28:229-34.

Methapyrilene: Calandre EP et al. 1981;29:527-32.

Terbutaline: Bredberg U et al. 1992;52:239-48.

Theophylline: Mitenko PA, Ogilvie RI 1974;6:720-6.

Miscellaneous agents

4-Aminopyridine: Uges DRA et al. 1982;31:587-93.

Clodronate: Yakatan GJ et al. 1982;31:402-10.

Dihydroergotamine: Bobik A et al. 1981;30:673-9; Woodcock BG et al. 1982;32:622-7.

Flumazenil: Janssen U et al. 1989;46:317-23.

Fluoride: Ekstrand J et al. 1978;23:329-37.

Indomethacin (indometacin): Alvan G et al. 1975;18:364-73.

Pentoxifylline: Beermann B et al. 1985;37:25-8; Rames A et al. 1990;47:354-9.

Warfarin: Breckenridge A, Orme M 1973;14:955-61.

d-Xylose: Worwag EM et al. 1987;41:351-7.