DRUG ENANTIOMERS AND THE ELDERLY: ONE DRUG OR TWO?

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INTRODUCTION

"All artificial bodies and all minerals have superimposable images. Opposed to these are nearly all organic substances which play an important role in plant and animal life. These are assymetric, and indeed have the kind of symmetry in which the image is not superimposable with the object."[1]

Chemical and pharmacological laboratories are generally misleading nonchiral environments, but the universe at its most fundamental level is handed, being made up of molecules, sugars and amino acids whose stereochemistry is absolutely defined. It is not therefore surprising that living organisms are able to discriminate between the two enantiomers of an exogenous chiral compound and large differences occur between the responses they evoke. It may seem strange that we have lost sight of a phenomenon whose importance was first made apparent 100 years ago.

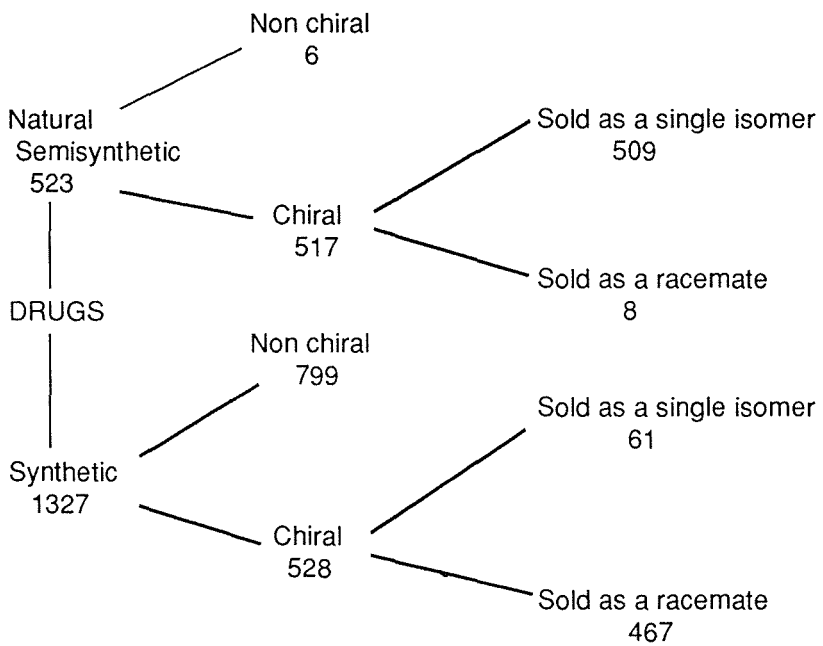
Selectivity in action is based on a chemical complementariness between the bioactive agents and their specific molecular sites of action, enzymes, specific receptors, carrier molecules and so forth. It concerns the physical-chemical characteristics of the groups in the molecule that participate in the interaction, as well as their spatial arrangement or

steric configuration[2].

Several drugs in present therapeutic use are racemates, since the time of their development there was little concern about stereoselectivity in drug action and disposition. Mason (1984) (Figure 1) has calculated that 82% of the synthetic chiral pharmaceuticals which appear in the USP are administered as their racemates i.e. as equal mixtures of relatively "active" and "inactive" isomers. The inactive form, however, may not be a passive component of the drug mixture. It may be an agonist, or an antagonist, or it may have actions on other receptors resulting in either unwanted side effects or contributing to overall drug efficacy. In addition, its metabolites may also be active or toxic.

Furthermore, even as a totally inactive, passive component, it may place unnecessary burdens on the body's clearance mechanisms.

Fig. 1. Chirality of drugs: their application as single isomers or racemates (derived from Kleeman and Engel (1982)[3] and Bailey (1986)[4])



HISTORY

In the 1930's British pharmacologist, Arthur R. Cushing, demonstrated substantial differences between the pharmacological properties of atropine, (±) hyosyamine and (-) hyosyamine. During the 1950's the importance of stereochemical considerations in medicinal chemistry and drug design was consistently emphasised by Arnold Beckett and Alan Casey in their classical studies on synthetic opiate type narcotics. However in the 1960's, to addition the therapeutic armaentarium of novel synthetic drugs was invariably in the racemic form[5]. Perhaps the tragic example is thalidomide. Marketed during the 1960's as a sedative, it was widely used by pregnant women, many of whom later gave birth to deformed children. Thalidomide was administered as a racemic mixture of its two optical isomers and only later research showed that the sinistral (-) isomer, but not the (±) isomer, has a tetratogenic effect on rat embryos.

TODAY

Present day medical curricula deal with stereochemistry as something to be mentioned only when dealing with the biochemistry of aminoacids and sugars. Few teaching and reference books even mention stereochemistry and its significance[2].

Today the use of chiral drugs requires the study of the pharmacokinetics and pharmacodynamics of each of the two enantiomers, not only on their own but also in combination with its antipode, before and after administration.

The rapid flow of published data regarding drug enantiomers is strongly indicating that studies on individual enantiomers should be quantiated individually for a number of reasons:

(a) Although not generally as extensive as differences in the intrinsic pharmacological activity of enantiomers, differences in the kinetics of these compounds may arise in all facets of their handling by the body. Enantiospecific pharmacokinetics are ignored at the risk of producing data which are open to misinterpretation, especially when attempting to relate drug concentration to response across species, and between and within different types of patients.

(b) Analytical tools aiming at characterising stereoisomers in terms of their configuration and conformation as well as their optical purity are becoming increasingly important in the field of chiral drug development. Chromatographic techniques (GC, HPLC, SFC, etc.) in particular have proved to be highly efficient in analysing the individual stereoisomers, thus enabling the determination of 'optical impurities' besides 'chemical impurities' in chiral drugs and formulations thereof. Pharmacokinetic studies as well as modern drug monitoring programs also need to be performed stereospecifically.

THE ELDERLY PATIENT

Drug action is modified by age at different levels. The table (Figure 2) shows some of the physiological changes produced by aging which may have important implications for altered pharmacokinetics[6]. The metabolite spectrum may alter with age; decrease in hepatic blood flow decreases hepatic clearance. Renal function is also subject to change with age as shown by the alteration of creatinine clearance. The concentration of serum albumin, hence the binding of several drugs in plasma, is significantly reduced in the elderly patient which may lead to increased susceptibility to multiple drug therapy. Keeping doses low should be beneficial in avoiding toxicity in the elderly.

At present there is a lack of collected data on whether the elderly population handle enantiomers in the same way as their younger counterparts, but potential areas for clinically important differences are numerous. These complex effects may explain some of the apparent paradoxes of drug treatment in the elderly, with toxicity at low plasma concentrations or ineffective high ones or increased sensitivity with apparent normal pharmacokinetics[6].

It must be noted, at this point, that some drugs are already being marketed as one enantiomer: Naprosyn® contains only the S(+)-enantiomer; resolution of dopa for the treatment of Parkinson's disease was shown to be therapeutically advantageous as the use of DL-Dopa was associated with a significant incidence of granulocytopenia, which was no longer a problem when only the L-enantiomer was used. Other catecholamines such as methyldopa and adrenaline are also used as one active enantiomer alone.

Fig. 2. Physiological changes with aging potentially affecting drug pharmacokinetics

Process	Type of Interaction
Absorption	Reduced gastric acid production Reduced gastric emptying rate Reduced gastrointestinal motility Reduced gastrointestinal blood flow Reduced absorptive surface
Distribution	Decreased total body mass Increased proportion of body fat Decreased proportion of body water Decreased plasma albumin Disease-related increase in α_1-acid glycoprotein Altered relative tissue perfusion
Metabolism	Reduced liver mass Reduced liver blood flow Reduced hepatic metabolic capacity
Excretion	Reduced glomerular filtration Reduced renal tubular function

Hexobarbital

Optical specificity may be altered by aging, resulting in disproportionate accumulation or clearance for one drug enantiomer or another.

The first reported demonstration of age related preferential decline in metabolism of one enantiomer over another was published in 1988[8]. The influence of age on stereoselective disposition of a single oral dose of racemic hexobarbital, 500mg, was investigated in 10 young (19-27) and 10 elderly patients (65-71).

Mean oral clearance of d-hexobarbital did not differ significantly between young and elderly volunteers. However, for (R)-hexobarbital mean oral clearance was about twofold greater in the young when compared with the elderly subjects.

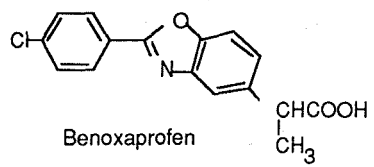
Non-steroidal anti-inflammatory drugs

An important class of chiral compounds are the nonsteroidal anti-inflammatory drugs (NSAID) with the 2-arylpropionic acid (APA) structure (Figure 3). The majority (if not all) of the potency of these drugs is associated with the (S)-configuration, the (R)-isomers having very little therapeutic effects (Figures 4, 5)[9].

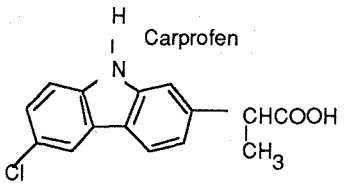
Ketoprofen has been marketed and used as a racemic mixture. In healthy volunteers, negligible differences have been reported between the plasma time courses of the two enantiomers (Figure 6)[10]. Using a stereospecific HPLC assay, measuring (R)- and (S)-ketoprofen in plasma and urine, the pharmacokinetics of the enantiomers, following a single (50mg) and then multiple (50mg every 6hr for 3 days) doses were determined delined in nine young and nine elderly arthritic patients. There were no significant differences between pharmacokinetic indices calculated after single and multiple doses, or between the two enantiomers. However, significantly, more conjugated (S)-ketoprofen was found in the elderly patient plasma. As the elimination of conjugated ketoprofen in both group patients was more extensive for the (S)- when compared to the (R)-, it is suggested that age dependent impaired elimination of conjugated (S)-isomer, along with preferential biliary excretion of conjugated (R)-ketoprofen is responsible for these observations.

The formation of conjugated ketoprofen seems to be dose dependent giving rise to saturable kinetics, and in elderly patients with compromised renal function, the conjugated drug will accumulate following saturable metabolism. The conjugated (R)-ketoprofen will have no difficulty leaving the systemic circulation via the biliary route, but the (S)-conjugate will accumulate as the dose increases. Upon saturation of the conjugated systems there may develop a competition for conjugation between the two isomers which may arise to substantially different concentrations for the isomers.

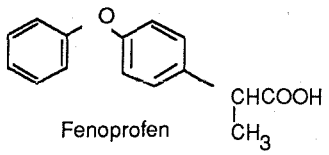
Fig. 3. Chemical structure of some 2-arylpropionic acid NSAIDs



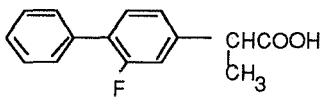
Benoxaprofen



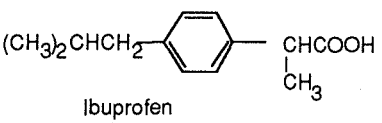
Carprofen



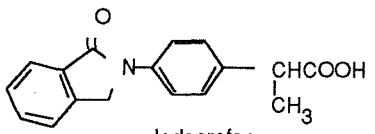
Fenoprofen



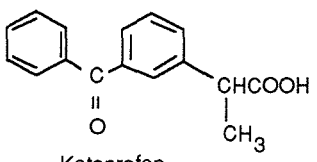
Flurbiprofen



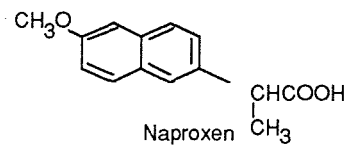
Ibuprofen



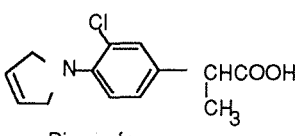
Indoprofen



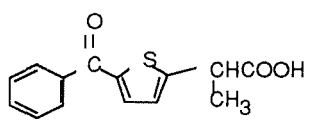
Ketoprofen



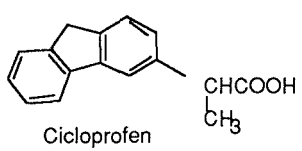
Naproxen



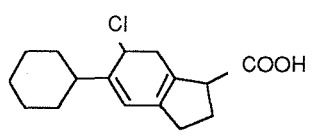
Piroprofen



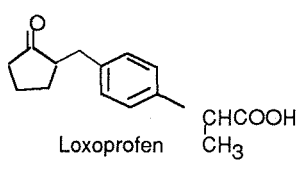
Tiaprofenic Acid



Ciclоprofen



Clidanac



Loxoprofen

Fig. 4. Plasma concentrations of enantiomers of ibuprofen in a healthy subject following a single 600 mg rectal dose. Key: diamonds, S-, and open squares, R-, enantiomers

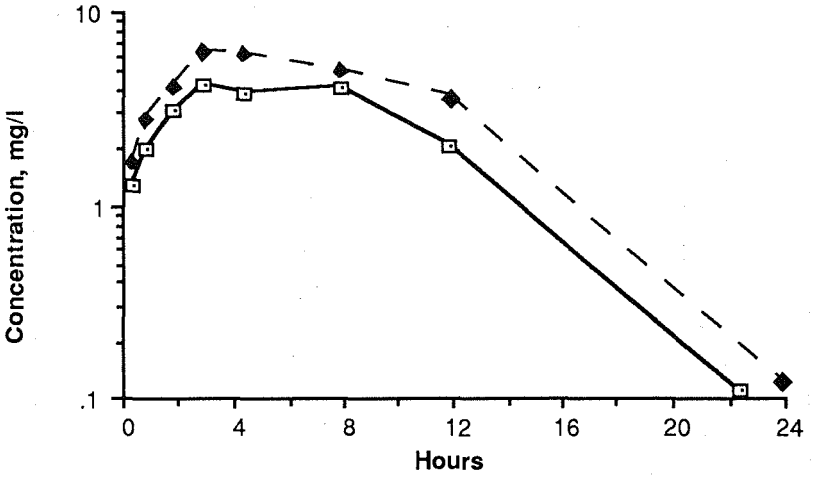


Fig. 5. Typical plasma S- (diamonds) and R- (open squares) fenoprofen concentrations in a subject after a single 300 mg oral racemic doses

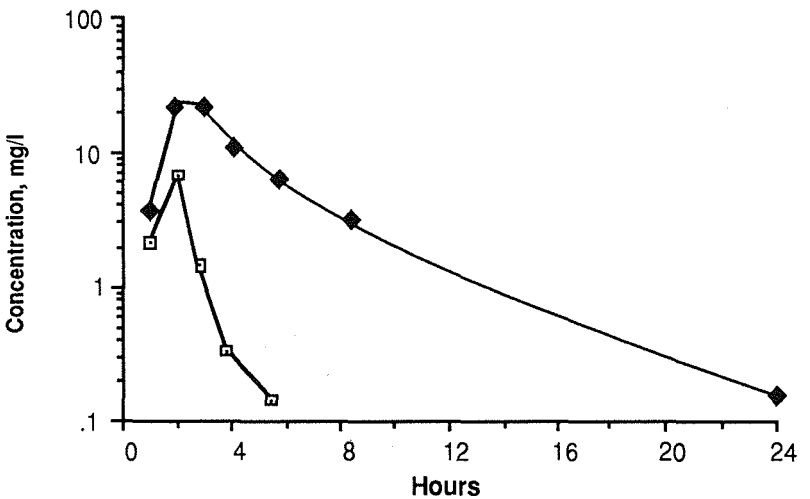
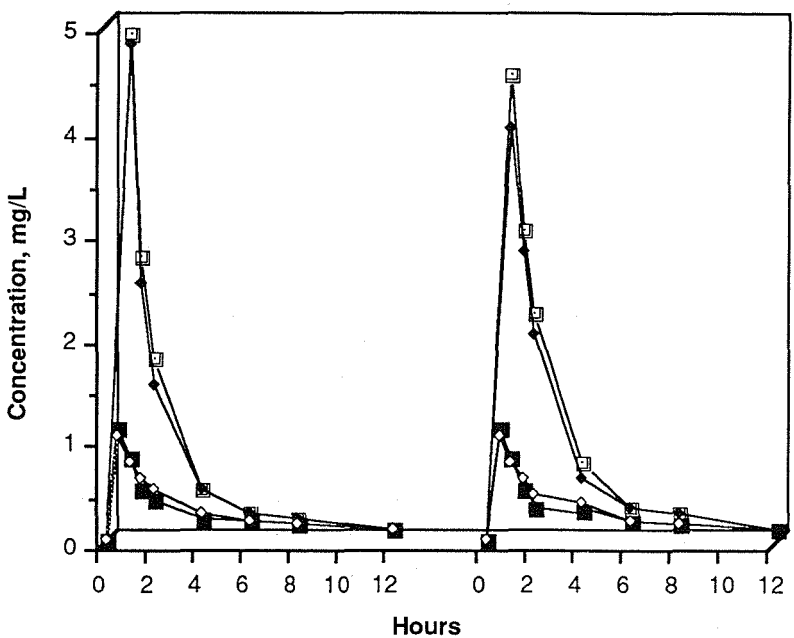


Fig. 6. Plasma-time courses of ketoprofen enantiomers (dark diamonds, S; open squares, R) and conjugated enantiomers (open diamonds, S; dark squares, R) following the first dose (A) and after achievement of the steady-state (B) in an elderly patient receiving 50 mg t.i.d. of racemic oral doses



Verapamil

Stereoselective first pass metabolism has also been shown for verapamil, the systemic availability of the more active (-) enantiomer being 2-3 times greater than that for the (+) enantiomer. This data explained the apparent paradox that when an IV and an oral dose of verapamil were titrated to give the same plasma concentration there was a 2-3 fold difference in pharmacodynamic response with respect to the dromotropic effect and atrioventricular condition. Such a phenomena must be considered in elderly patients as slower gastric empyting time increases degradation and may lead to abnormally low plasma concentrations for oral doses.

PROTEIN BINDING

There may also be alterations in optical specificity of protein binding or displacement, particularly if the binding proteins are in short supply. Uremia in elderly patients has been found to decrease the binding of (R)-flurbiprofen preferentially (Figure 7)[11].

Fig. 7. Binding of racemic flurbiprofen to protein in human plasma

	Percent unbound ± S.D.	Min.	Max.	Albumin ± S.D. (g/dl)
Normal ($n = 9$)	0.050 ± 0.006	0.043	0.060	4.51 ± 0.34
Renal insufficiency ($n = 5$)	0.068 ± 0.012*	0.047	0.092	4.13 ± 0.45
Liver disease ($n = 5$)	0.054 ± 0.019	0.042	0.086	3.93 ± 0.56
Elderly ($n = 15$)	0.053 ± 0.005	0.042	0.059	4.39 ± 0.44
Obese ($n = 15$)	0.050 ± 0.010	0.041	0.067	4.02 ± 0.42
Hypoalbuminemic ($n = 4$)	0.187 ± 0.159*	0.084	0.423	2.46 ± 0.54*

* Significantly different from normal volunteers, $P < 0.05$

REGULATIONS

In view of the pronounced differences in activity and disposition which can exist between enantiomers, two drugs are in fact being administered. Recognition of this aspect has stimulated a lively debate as to whether the racemic drugs in therapeutic use should still be used as racemates or whether such drugs should be replaced by drug preparations containing only the active enantiomer. In assessing the merits and benefits one must consider what is to be gained in terms of therapeutic efficacy and safety if a stereochemically pure instead of a racemic drug were to be used.

The regulatory authorities are beginning to respond to the scientific and clinical maelstrom concerning the issue of racemates and enantiomers. In the US, the FDA has an ongoing discussion with industry which is

likely to lead to the promulgation of guidelines. Matters are further advanced in Europe where at present the Committee for Proprietory Medical Products is considering a draft guideline statement on isomerism for inclusion in its "Notice to Applicants". If adopted, as looks likely, new submissions for drugs with chiral centres will have to provide information, interalia, on the following points: isomer ratio and batch to batch consistency; a discussion of the toxicological and pharmacological properties of the isomers, enantiomer-specific metabolism and kinetics and the extrapolation of preclinical data (particularly if species difference occur in the handing of stereoisomers); and a discussion of possible clinical problems that may arise in relation to stereoisomers.

In Japan the health authorities, in meetings with the pharmaceutical industry, have explained their requirements in the context of the registration of a racemic mixture or optical isomer. Basically, for a racemic mixture, information will be required in the toxicity pharmacology (efficacy and general) and the disposition of each isomer and on the extent of the interconversion of the two isomeric forms. Lastly, information will be required in isomer purity; if one of the isomers constitutes a major 'impurity' then this will have to be fully studied in terms of toxicity, pharmacology and disposition[5].

CONCLUSION

Should chiral drugs be used as a singler isomer?

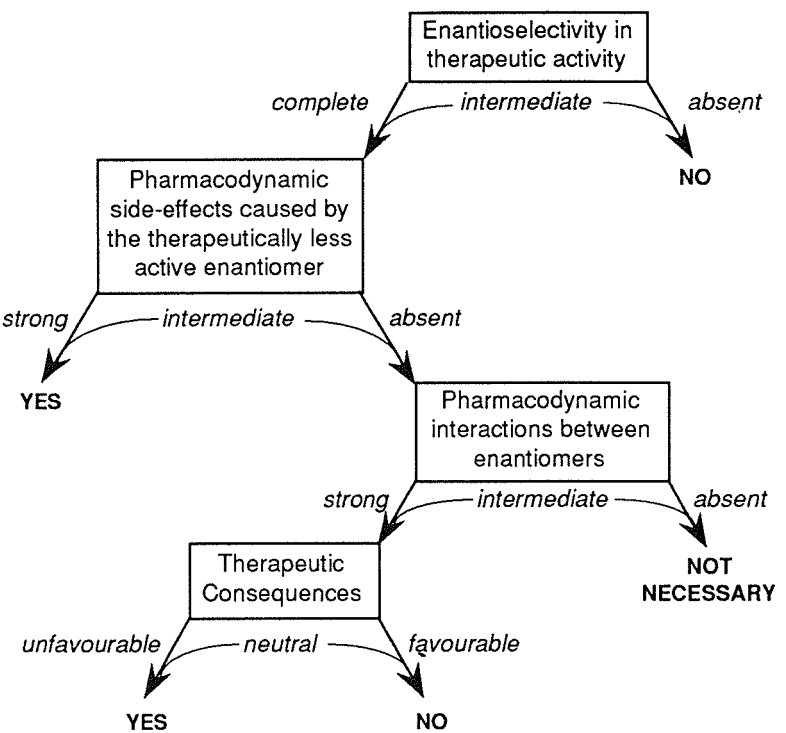
The cost of developing a new medicine is high and increasing. For the relatively few products which are medically and commercially successful today, many thousands of would-be drugs have fallen by the wayside.

The production of optically active drugs in place of racemates does not seem to be a profitable venture. It would increase production costs and to state bluntly that racemic drugs contain a 50% impurity is a gross simplification. Many scientific factors should be taken into account before, and they require a wealth of information which is not always available. Chiral aspects of new drug entitites have had a profound influence on development activities within the pharmaceutical. Criteria addressed in the decision to develop a racemate or single stereoisomer

include pharmacological, toxicological and pharmacokinetic differences between the isomers, therapeutic ratio cost of large scale production, feasibility and chiral inversion, therapeutic need, novelty of drug product, etc. Such issues have necessitated utilizing greater time and cost resources in drug development problems than those normally expended for conventional drugs. Decisions on whether the racemate or enantiomer is developed for marketing should, in our opinion, be taken on a case by case basis[5].

All in all, this probably argues for some sort of 'decision tree' approach to the issue, incorporating factors such as pharmacological and toxicological properties of the enantiomers, pharmacokinetic properties, interactive potential, feasibility and cost of production, quality control criteria and 'marketing edge'[12] (Figure 8).

Fig. 8. Proposed logical scheme addressing the question: 'Should chiral drugs be used as a single enantiomer?'



Some may find all this somewhat daunting. Nevertheless, the realization of the importance of stereochemistry in pharmacology, in our opinion has an important contribution to make to the development and use of safer and more effective medicines.

To conclude: a basic rule in science is "non capability or impossibility to do things the proper way is no excuse to do them the wrong way[2].

REFERENCES

1. Pasteur L (1901). On the assymetry of naturally occuring organic compounds, the foundations of stereochemistry. In: Memoirs by Pasteur, Van't Hoff, Le Bel and Wislicenuss (Richardson GM eds.) American Book Company, New York.
2. Ariens EJ (1987). Implications of the neglect of stereochemistry in pharmacokinetics and clinical pharmacology. Drug Int. Clin. Pharm., 21: 827-829.
3. Kleeman A, Engel J (1982). Pharmazeutische Wirkstoffe. Thieme Verlag. Stuggart/New York.
4. Bailey DM (ed). Annual Reports in Medicinal Chemistry, Vol 19-21. Academic Press, 1983-1986.
5. Smith RL, Caldwell J (1989). Racemates: towards a new year resolution? Trends in Pharmacological Sciences, 1: 75-77.
6. Dawling S, Crome P (1989). Clinical pharmacokinetics in the elderly - an update. Clin. Pharmacokin, 17 (4): 236-263.
7. Williams K, Lee E (1985). Importance of drug enantiomers in clinical pharmacology. Drugs, 30: 333-354.
8. Chandler MH, Scott SR, Boulin RA (1988). Age associated alterations in hexobarbital metabolism. Clin. Pharmacol Ther, 43: 436-441.
9. Jamali F (1988). Pharmacokinetics of enantiomers of chiral nonsteroidal anti-inflammatory drugs. Eur. J. Drug Met. and Pharmco., 13: 1-9.
10. Foster RT, Jamali F, Russell AS, Alballa SR (1988). Pharmacokinetics of ketoprofen enantiomers in young and elderly arthritic patients following single and multipe doses. J. Pharm. Sci., 77: 191-195.
11. Knadler MP, Brater DC, Hall SD (1989). Plasma protein binding of flurbiprofen: enantioselectivity and influence of pathophysiological status. J. Pharmacol. Exp. Therap., 249: 378-385.