STEREOISOMERIC PHARMACOVIGILANCE AND RACEMIC DRUGS IN HOSPITAL FORMULARIES

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Summary

The rapid emergence of published data regarding drug enantiomers should be reflected in the use of racemic drugs in the clinical setting. The Department of Pharmacy, University of Malta, becoming aware of the problems created by the unknowledgeable use of racemic drugs has conducted two studies. The first study data focused on quantifying the number of chiral drugs in the Maltese National Formulary, being administered as racemic mixtures, in order to provide a better basis for purchase specifications when procuring drugs. The second study analyzed attitudes by physicians towards drug chirality.

Keywords

Enantiomers, chirality, stereoisomerism, pharmacovigilance, racemic drugs.

Introduction

The realization of the importance of stereochemistry in pharmacology and therapeutic action has a valid contribution to make in the development of safer and more effective medicine[1]. Such new knowledge should be reflected in the use of racemic drugs. Both the scientific and popular press have focused their attention on the upsurge in stereoisomeric interest - some with 'alarmist' headlines[2,3,4,5,6,7]. This should provide a better basis for purchase specifications of drugs and the promotion of stereoisomeric awareness amongst authorities and members of the health care team.

Stereoisomeric Drugs

Racemates are 50/50 mixtures of the left and right-handed forms or enantiomers of compounds, whose molecular structure lack symmetry because the central carbon atom is surrounded by four different atoms or groups of atoms. This phenomenon is referred to as chirality - derived from the Greek word *'cherios'* which signifies handedness i.e. being left or right handed. Enantiomers are mirror images and can be distinguished from the way they rotate polarized light, hence the (+)/(-) or (d)/(l) nomenclature. The accepted nomenclature today is the (R)/(S) system which is related to the Cahn-Ingold-Prelog Convention[7]. For example labetolol is only one of a number of chiral drugs with two chiral centers (figure 1). Often one isomer is therapeutically active but this does not mean that the other is inactive. The therapeutically nonactive form in a racemate may be regarded as an impurity but it 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[2].

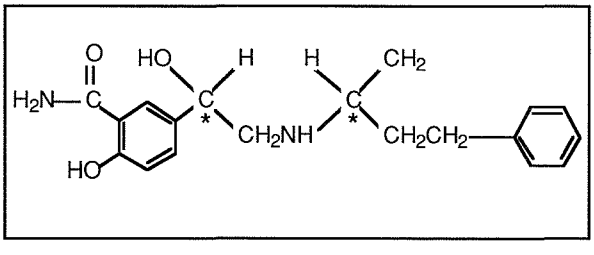

Figure 1: The chemical structure of labetolol. (*chiral centres).

Perhaps the most dramatic example is highlighted by the thalidomide tragedy. This drug was marketed during the 1960's as a sedative, and 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. Too late, did subsequent research show that it was only the sinistral (-)-isomer, and not the (+)-isomer, which had a teratogenic effect on rat embryos, producing the same birth defect as those of the thalidomide children in the early 1960's [8].

About 40% of synthetic drugs are chiral. Mason[9] has calculated that more than 80% of the synthetic chiral pharmaceuticals which appear in the United States Pharmacopoeia are administered as their racemates i.e. as equal mixtures of relatively 'active' and 'inactive' isomers. Terms such as isomeric ballast[2] and composite chiral drugs (CCDs)[10] have now become commonplace. But unfortunately medical curricula still deal with stereochemistry as an area to be investigated only when referring to the biochemistry of amino acids and sugars. Few teaching and/or reference medical books ever mention stereochemistry and its significance[1].

Methods

Study 1

A comprehensive database was compiled of all drugs in the updated version of the Maltese National Formulary, subclassified as synthetic, semisynthetic and natural, chiral and achiral and including stereochemical properties, efficacy, risk benefit, and cost effectiveness of single isomers of drug racemates (if available). Standard textbooks such as *Martindale*[11], *British Pharmacopoeia*[12] and *Therapeutic Drugs*[13] were used to determine the structure of each drug and whether it was available as single enantiomer or not.

Study 2

A survey was conducted on a randomized sample of registered physicians in Malta in order to review their attitudes towards inherent problems associated with the use of racemic drugs. The thesis behind the study expounded on Tucker's presupposition that most clinicians are unlikely to 'know their right hand from their left'[3].

Results

Study 1

From an in-depth scrutiny, it was revealed that approximately 47% of drugs in the Maltese National Formulary classified as semisynthetic/natural; 99% of these had at least one chiral center but nearly all were available as one isomer, while more than 60% of synthetic chiral drugs were purchased as racemates (figure 2, figure 3). The distribution of racemic drugs amongst different pharmacological categories was found to be highly uneven. The appearance of a racemate in the field of peptides or hormones was exceptional.

The study also included a separate review of geometric isomers, such as tamoxifen and phytomenadione, which had previously been pooled with chiral isomers. These made up about 3% of the total number of drugs (figure 4). Problems associated with the use of the wrong isomer of tamoxifen had already been described in our hospital[14].

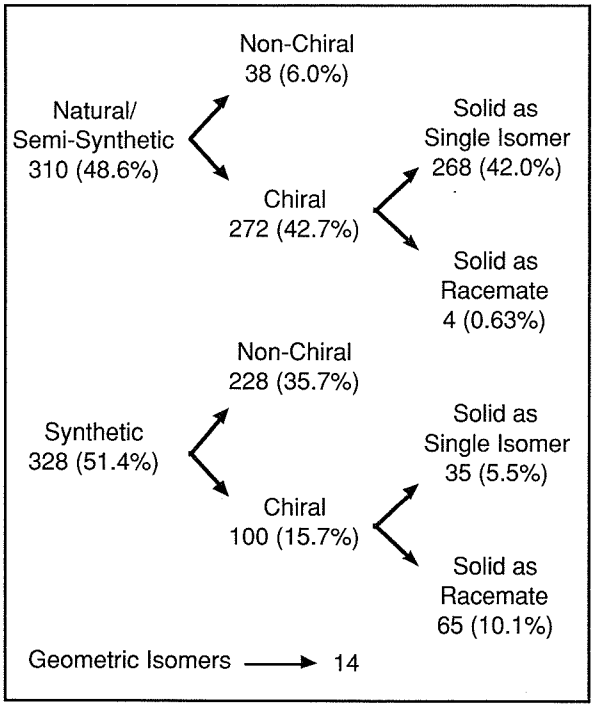

Figure 2: The chirality of drugs in the Maltese Formulary.

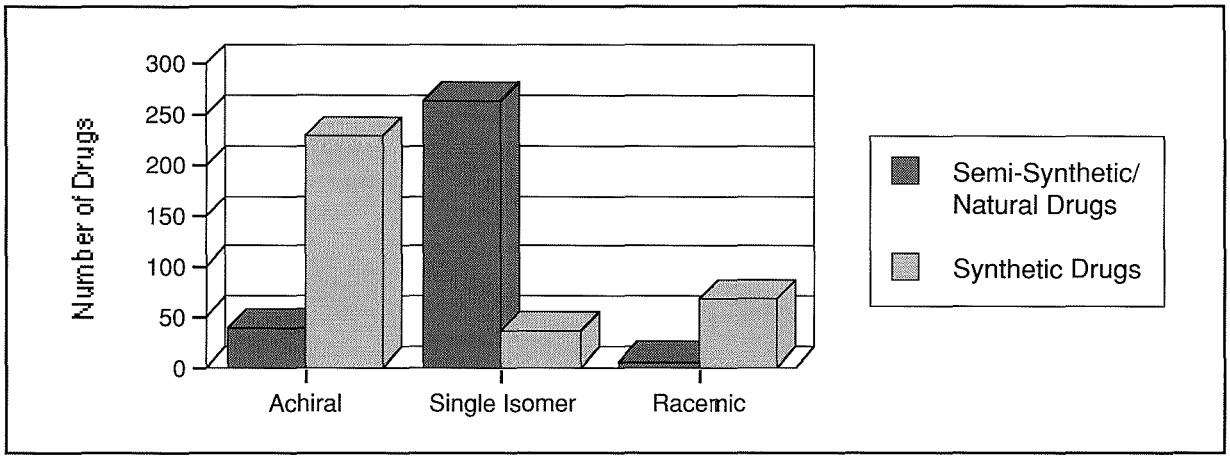

Figure 3: A comparison of the stereoisomeric configuration of organic drugs in the Maltese Formulary.

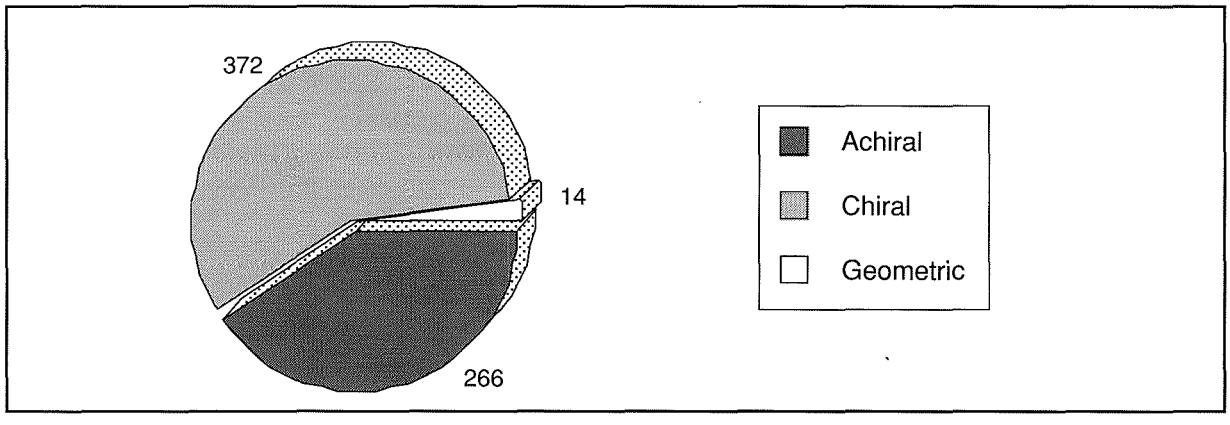

Figure 4: Subdivision of organic drugs found in the Maltese Formulary.

These results were consistent with previously published data [15,16,17]. Most racemic drugs are now under investigation and the pharmacokinetic and pharmacodynamic differences studied. Only a few synthetic chiral drugs e.g. naprosyn, timolol, methyldopa, and dextromethorphan are already available as a single enantiomer[1,18,19].

A review of published literature was undertaken to evaluate when the use of single isomers is recommended. References were found to indicate large pharmacological differences in quite a large number of chiral drugs[19]. It has been reported that it is (d)-propranolol which acts as the beta-adrenoreceptor agent, but both stereoisomers contribute to its local anesthetic and histamine releasing action[20]. (d)-Ketamine is predominantly a hypnotic and an analgesic, whereas the (l)-isomer is the main source of its unwanted side-effects [21]. The therapeutic index of disopyramide could be improved by eliminating the (-)-isomer. This enantiomer is a less potent anti-arrhythmic then the (+)-form, and it is mostly responsible for the heart failure precipitated by administration of the racemic drug, through its marked negative inotropic effect [22].

Care must be exerted if decisions are taken to change from a racemate to an isomer. Although the (S)-isomer of warfarin is about 3-5 times as potent as its antipode, switching from the racemate to the (S)-isomer, would necessitate a reduction in the dose. There would be no change in therapeutic index and this would precipitate a specific set of potential drug interactions[23]. On the contrary, the greater intrinsic anti-inflammatory potency of (S)-ibuprofen is compensated to some extent when using the racemate by metabolic inversion of the less active (R)-form and in fact approximately 60% of an oral dose of (R)-ibuprufen is inverted to the (S)-enantiomer [24]. Drugs available as single isomers were often prohibitively expensive compared to their racemic counterparts. Cost effectiveness of the use of single isomers is still to be determined.

The results and recommendations of this study are to be handed over to the Maltese Drugs and Therapeutic Committee, which is responsible for updating the Maltese National formulary and also to the Drug Information Unit, at St. Luke's Hospital, the major teaching hospital in Malta.

Study 2

A survey was made among a randomized sample of registered physicians in Malta. Over 320 questionnaires were sent by post. There was a 33% response, consistent with previous surveys of this type and it reflected the actual population of Maltese physicians. Nearly 40% of these graduated 5-10 years ago (figure 5). The respondents were mostly housemen (21%) or consultants (23.1%). 28% worked in the community, while 10% were retired (Figure 6); 66.2% regularly attended continuing education courses.

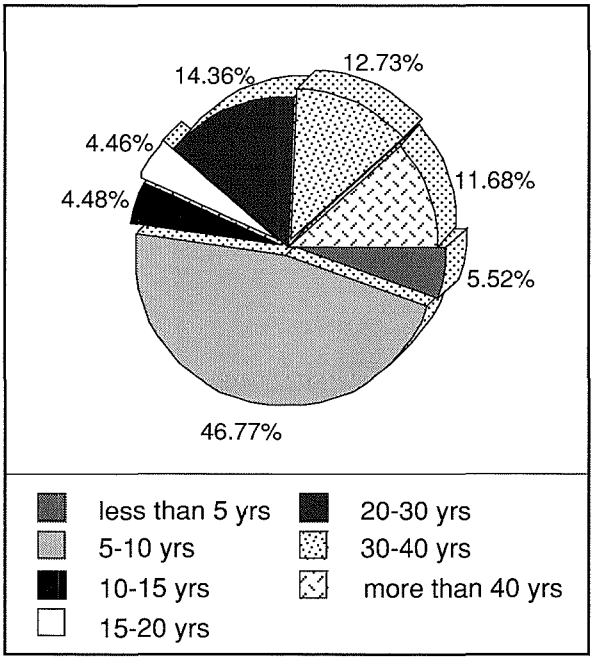

Figure 5: Registration year of physicians who responded.

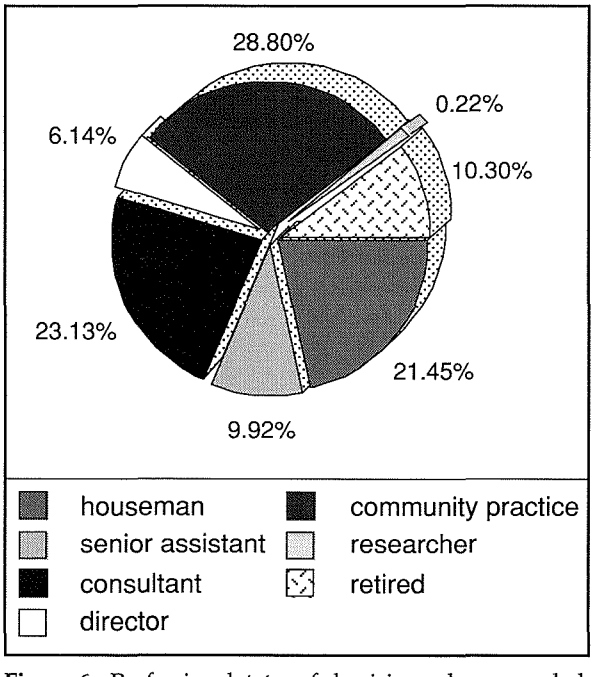

Figure 6: Professional status of physicians who responded.

When questioned about the terms stereoisomerism and chirality, 52% said that this topic had only been mentioned briefly in their undergraduate years, mostly in their biochemistry and pharmacology courses. Less than 10% had heard the terms in postgraduate training or continuing education courses (Figure 7). Two doctors referred to the use of (-) folic acid and importance of stereoisomerism in legal definitions of drugs of abuse. 83% had never read any information about drug chirality while 11% had read at least one article in the medical literature. Only in 2 cases, had the subject been mentioned by a drug medical representative (Figure 8).

Were the terms *Stereoisomerism* or *Chirality* ever mentioned ?

	Yes	No
Undergraduate Years	52.00%	48.00%
Postgraduate Years	9.88%	90.12%
Continuing Education	5.82%	94.18%

Figure 7: Physicians' knowledge of chirality.

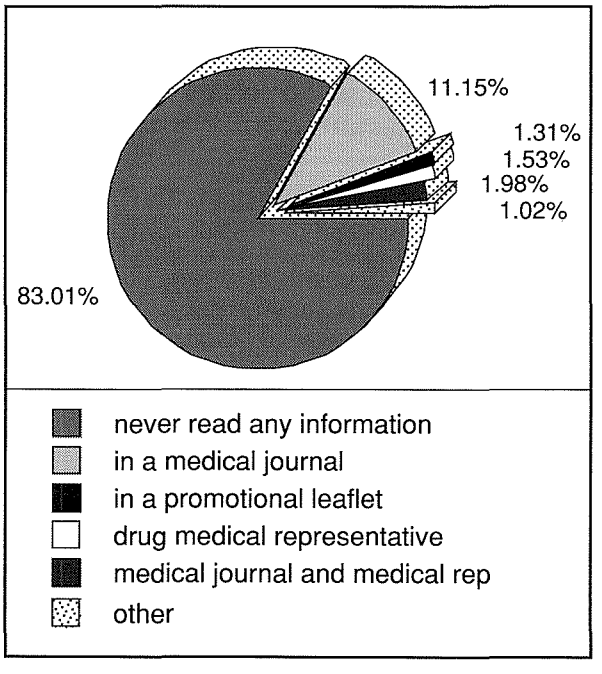

Figure 8: Physicians' sources of information on chirality.

43% were of the opinion that these problems should be tackled by physicians, pharmacists and biochemists, and some even suggested that it should be tackled by the local authorities and the pharmaceutical industry (Figure 9). It was interesting to note that nearly all were grateful for the information we had given them and 92% wanted to learn more about the subject, especially by receiving more information at home or attending a lecture. Some respondents were keen to participate in continuing education sessions on the subject (Figure 10). Only a small percent of physicians (<13%) questioned were actually aware of the problems associated with administering drug racemates (Figure 11). Nearly all the doctors found the subject very interesting and even showed their professional gratitude for the study.

Interested in learning more about drug chirality	**92.26%**
More literature at home	62.06%
Read more about it in medical journals	27.52%
Attend organised lectures	15.72%
Part of continuing education course	33.31%

Figure 10: Respondents' interest to further knowledge.

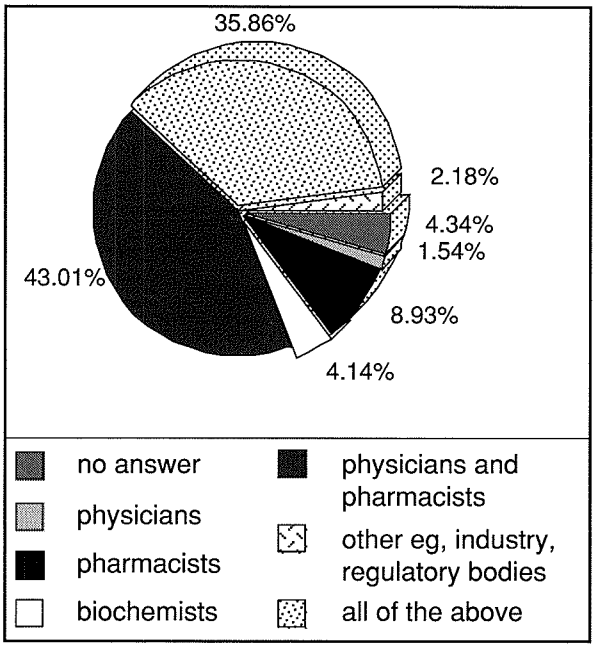

Figure 9: Members of the health care team who, according to physicians, should tackle the problem.

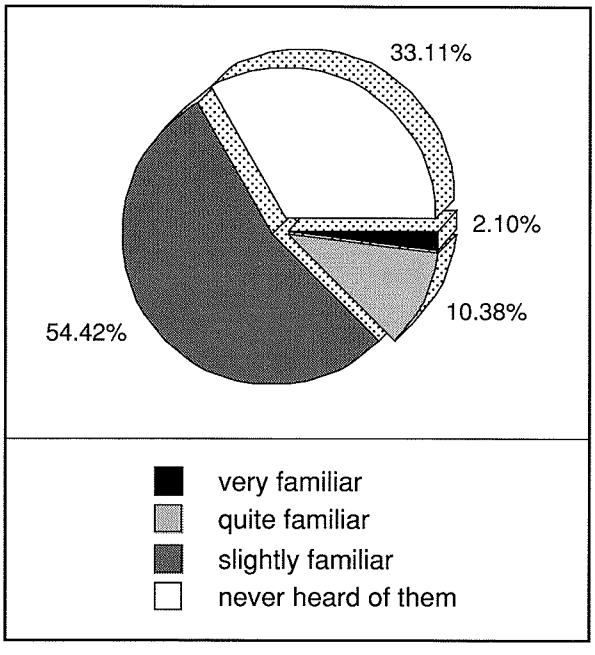

Figure 11: Physicians' familiarity with the terms *stereoisomerism* and *chirality*.

Conclusion

Most chiral synthetic drugs are still widely used as racemic mixtures in the clinical setting even if published literature suggests pharmacological differences. It can be argued that the majority of physicians are still unaware of problems associated with administering racemic drugs, but it appears from this study that most are willing to learn more. Several regulatory agencies have issued guidelines[25,26,27,28]. Perhaps it is wrong to start a witch hunt for racemic drugs which are already marketed[29], but it can be predicted that a full clinical study of the pharmacological and toxicological effects of both enantiomers of any new chiral drug, may be required soon, in order to obtain authorization for marketing the drug as a racemic mixture [30](Figure 12). Only 5 of the 12 leading chiral drugs in the USA are being sold as single isomers. Some drugs are already being developed as the pure enantiomers from existing composite chiral drugs with still valid patents. These include S-atenolol, R-salbutamol, S-terfenadine, R-ketoprofen, RR-formoterol, S-fluoxetine, S-ondansteron, R-salmeterol, S-fluriprofen and S-ibuprofen. Some drugs such as fenfluramine, are being sold simultaneously as a single isomer (Adifex^{R}) and as a racemate (Ponderax^{R}). The less

cardiotoxic R-isomer of verapamil is being investigated for the prevention of MDR in cancer chemotherapy.

Stereoisomeric pharmacovigilance on the use of racemic drugs should be encouraged and the new EU and FDA regulations translated to the clinical setting[31] but it appears that, so far, little has been done. In very few of the recommended textbooks of pharmacology, pharmacokinetics and toxicology, are the principles of stereoselectivity properly described or even mentioned in the index, although some specialized pharmacy journals have included the subject in continuing education articles for their readers[32,33]. Financial restraints often dictate health policies and procurement procedures. However, stereoisomeric pharmacovigilance on the use of racemic drugs in hospital formularies must be encouraged. Appropriate education is needed if choices between racemates and single isomers are to be presented. Drug therapy can only gain from the fruitful discussions on the continual assessment of **'looking glass drugs'**, and to Tucker's challenge 'Does the left hand know what the right hand is doing, we ask ' Does the left hand want to know what the right hand is doing'. The answer from Malta is an unequivocal grateful 'yes'.

Arguments in favour of marketing drugs as pure enantiomers
• Improved less complex and more selective pharmacological profile • Better therapeutic index • Less complex pharmacokinetics • Less complex concentration-response relationships particularly in relation to therapeutic drug monitoring
Arguments against marketing drugs as pure enantiomers
• Cost of development • Cost of production

Figure 12: Enantiomers or Racemates?[30]

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