THE CHIRAL SWITCH:
THE DEVELOPMENT OF SINGLE ENANTIOMER DRUGS
FROM RACEMATES

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Over the last ten to fifteen years drug chirality, particularly the use of single enantiomers versus racemic mixtures, has become an area of considerable interest. As a result of advances in the chemical technologies associated with the synthesis, separation and analysis of the individual enantiomers present in a racemate, together with regulatory requirements the number of chiral drugs presented for approval to regulatory authorities as single enantiomers rather than racemates has increased. In addition to new chemical entities a number of “old” racemates have been re-evaluated as potential single enantiomer products with the possibility for an improved therapeutic profile. These so-called Chiral Switches have resulted in a number of agents being commercially available as both single enantiomer and racemic mixtures at the same time. However, not all these re-evaluations have resulted in the expected therapeutic benefits and unpredicted adverse reactions have resulted. The issues, both economic and therapeutic, associated with the Chiral Switch process are addressed in this article.

Key words: chiral switch – stereoisomers – racemates – enantiomers

INTRODUCTION

In recent years there has been considerable interest in the biological activity, both pharmacological and toxicological, of the enantiomers of chiral drugs. This interest in drug stereochemistry has resulted from the considerable advances in the synthesis [1,2], analysis and separation [3-9] of chiral molecules, together with an increased appreciation of the potential significance of the differential biological properties of the enantiomers of chiral drugs administered as racemates [10-16]. As a result of these advances in technology and the potential benefits of single enantiomer drugs
(summarized in Table 1), drug stereochemistry became an issue for the pharmaceutical industry and the regulatory authorities [17-20]. A number of scientific meetings, involving academic, industrial and regulatory scientists, were held in the late 1980s – early 1990s with the specific objective of discussing the new technologies and the significance of chirality in pharmacology and therapeutics [21-23].

Table 1. Potential advantages of single enantiomer products [16]

<table>
<thead>
<tr>
<th>Advantage</th>
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<tr>
<td>Less complex, more selective pharmacodynamic profile</td>
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<td>Potential for an improved therapeutic index</td>
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<tr>
<td>Less complex pharmacokinetic profile</td>
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<tr>
<td>Reduced potential for complex drug interactions</td>
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<tr>
<td>Less complex relationship between plasma concentration and effect</td>
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In 1992 the Food and Drug Administration (FDA) in the USA published a policy statement for the development of new stereoisomeric drugs [24], which was closely followed by European guidelines in 1993, which came into force in 1994 [25]. At present there is no absolute requirement from any of the major regulatory authorities for the development of single enantiomer drugs and the decision regarding the stereoisomeric form, i.e. single enantiomer or racemic mixture, to be developed is left to the compound sponsor. However, the decision taken requires scientific justification based on quality, safety and efficacy, together with the risk-benefit ratio and may be argued on a case-by-case basis [25].

As a result of regulatory attitudes, and associated technological developments the number of new chiral chemical entities as single stereoisomers, rather than racemic mixtures, submitted for approval to various regulatory bodies over the last ten years has increased and the trends for future drug development are evident [25,26]. However, in addition to new agents a number of established drugs marketed as racemates, have been re-evaluated and re-marketed as single enantiomers [27]. As a result both single enantiomer and racemic mixture products of the same ‚drug‘ are both available in a number of countries. It is obviously important that both pharmacists and physicians are aware that both single stereoisomer and mixture products are available and that they are able to compare their relative merits. The aim of this article is to examine these so-called Chiral Switches.

THE CHIRAL SWITCH

A racemic or chiral switch may be defined as the development of a single enantiomer from a previously marketed racemate [27]. Frequently the marketed single enantiomers have the same, or very similar, therapeutic indications as the originally marketed racemate but this may not always be the situation and novel indications for
"old" compounds have been reported. The chiral switch process has resulted in a number of agents being re-marketed as single enantiomer products (Fig. 1) and a summary of these agents, together with their reported therapeutic advantages, is presented in Table 2.

Fig. 1. Marketed single enantiomers of agents which have undergone the chiral switch

The idea of investigating single stereoisomers following the observation of unacceptable adverse effects with the racemate, or developments in technology enabling the production of a single stereoisomer is not new. For example D-penicillamine, introduced originally for the treatment of Wilson’s disease [28] has been used by rheumatologists for number of years [29]. The toxicity of the L-enantiomer to animals, including weight loss, intermittent fitting and death, has been known since the 1950s.
and, more recently the greater mutagenic potency of L- compared to D-penicillamine has been reported [30]. In the initial clinical evaluation of the drug for the treatment of Wilson’s disease in the USA, the use of the synthetic racemate resulted in optic neuritis [31] and the drug was withdrawn. In the UK, D-penicillamine was obtained as the single enantiomer, by the hydrolysis of penicillin, and the adverse effect was not observed [32].

Similarly the initial use of racemic dopa for the treatment of Parkinson’s disease resulted in a number of adverse effects, including nausea, vomiting, anorexia, involuntary movements and granulocytopenia [33]. The use of L-dopa resulted in halving the required dose, a reduction in adverse effects, granulocytopenia was not observed with the single enantiomer, and an increased number of improved patients [34].

The progestogen norgestrel, used as an oral contraceptive and in hormone replacement therapy, the activity of which resides in the laevorotatory enantiomer was initially marketed as a racemate in the mid-1970s. Subsequently, following developments in the synthetic methodology, the single enantiomer levonorgestrel was marketed in 1979. Both the single enantiomer and racemate are commercially available and used either alone or as components of combination products.

When single enantiomers are developed from previously marketed racemates the regulatory bodies permit bridging studies between the original and new submission [25]. Obviously potential difficulties may arise if the sponsor of the single enantiomer was not responsible for the original submission [25]. These investigations should include a comparison of the pharmacokinetic profile of the single enantiomer following administration as such and as a component of the racemate. Such studies ensure that interactions between the enantiomers present in the racemate do not occur resulting in differences in the pharmacokinetic parameters of the selected stereoisomer. For example in the case of citalopram the pharmacokinetic profile of both the drug and the desmethyl metabolite of the S-enantiomer (escitalopram) have been shown to be bioequivalent following oral administration of tablet formulations containing 40 mg of the racemate or 20 mg of escitalopram [35]. Similarly toxicological bridging studies in animals with both the single enantiomer and racemate showed a similar profile and the data derived with the racemate could be extrapolated to the stereoisomer [36].

In addition to the agents indicated in Table 2 a number of other compounds are undergoing evaluation as single enantiomer products, some of which are at a fairly advanced stage of development [27]. These include: (R,R)-formoterol for the treatment of asthma with the reported advantage of reduced airway hyperreactivity; (S)-oxybutinin, for the treatment of urinary incontinence with a reduction in anticholinergic side effects [37,38]; (S)-doxazosin for use in benign prostatic hyperplasia with the advantage of a reduction in orthostatic hypotension; (S)-lansoprazole and (-)-pan-toprazole for the treatment of gastro-oesophageal reflux; (+)-norcisapride for the treatment of nocturnal heartburn with a reduction in cardiotoxicity; eszopiclone for the treatment of insomnia; (S)-amlodipine for the treatment of hypertension with the advantage of a reduction in side effects; (S)-fluoxetine for use in migraine prophylaxis, phase II clinical trials indicating a reduction in attack frequency earlier and greater in comparison to placebo controls [39].
<table>
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<tr>
<th>Drug</th>
<th>Action/Indication</th>
<th>Comment</th>
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<tr>
<td>Dexketoprofen</td>
<td>Non-steroidal anti-inflammatory drug</td>
<td>Inhibition of cyclooxygenase activity resides in the S-enantiomer, unlike (R)-ibuprofen, (R)-ketoprofen undergoes minimal chiral inversion in humans (less than 10%) [76]. Reduced dose requirement in comparison to the racemate; formulation as the trometamol salt results in more rapid absorption and onset of action compared to the racemic free acid; reduced potential for gastric ulceration in animals [76].</td>
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<tr>
<td>Dexibuprofen</td>
<td>Non-steroidal anti-inflammatory drug</td>
<td>Main activity, inhibition of cyclooxygenase, resides predominantly in the S-enantiomer [72]. Following administration of the racemate (R)-ibuprofen undergoes partial chiral inversion (approximately 60%) to the active S-enantiomer [73]. A statistical evaluation of six clinical trials involving a variety of conditions, including backpain, joint pain, rheumatoid arthritis and ankylosing spondylitis, indicated that treatment with the single enantiomer (1200 mg daily) to be equivalent to, or better than, the racemate (2400 mg daily) [74]. The mean daily dose of dexibuprofen in patients with rheumatoid arthritis was reduced by approximately one third compared to the racemate [75]. A post marketing surveillance study in 1400 patients has indicated that dexibuprofen is a highly effective NSAID with a low adverse effect profile [102]. Single enantiomer preparations are available in Austria and Switzerland.</td>
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<tr>
<td>Esomeprazole</td>
<td>Proton pump inhibitor</td>
<td>S-Enantiomer of omeprazole; lower first pass metabolism, slower plasma clearance and increased systemic availability compared to the R-enantiomer [65]. Clinical evidence that the single enantiomer maintains intragastric pH above 4 in patients with gastro-oesophageal reflux disease significantly longer, with a 24 median intragastric pH greater than an equal dose of the racemate [65,86,87]. Reduction in interpatient variability in response [88].</td>
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<tr>
<td>LevoFloxacin</td>
<td>Antimicrobial</td>
<td>Quinolone derivative the activity of which resides in the S-enantiomer [67-70] modest differences in enantiomeric disposition favour the single enantiomer [70,71].</td>
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<td><strong>Levobupivacaine</strong></td>
<td><strong>Local anaesthetic</strong></td>
<td>Enantiomers of bupivacaine exhibit stereo-selectivity with respect to blockade of sodium and potassium ion channels, the $R$-enantiomer being more potent [77,78]. The cardiotoxicity of the drug appears to be predominantly associated with the $R$-enantiomer, <em>in vitro</em> investigations have indicated smaller conduction changes following treatment with the $S$-enantiomer in comparison to either ($R$)-bupivacaine or the racemate [79]. Following intravenous infusion of the racemate or $S$-enantiomer to healthy volunteers a significantly reduced negative inotropic effect (approximately half) was observed with the single enantiomer compared to the mixture [80]. Clinical studies have indicated that sensory block and the clinical profile following the single enantiomer are essentially the same as the racemate [81]. Thus, the single enantiomer results in a similar clinical profile with a reduction in cardiotoxicity [82].</td>
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<tr>
<td><strong>Escitalopram</strong></td>
<td><strong>Selective serotonin reuptake inhibitor</strong></td>
<td>$S$-Enantiomer of citalopram a potent selective serotonin reuptake inhibitor which in <em>in vitro</em> test systems is between 130 and 160 fold more potent than the $R$-enantiomer [94]. Clinical studies in depressed patients have indicated as much improvement with 10 mg daily of the single enantiomer as achieved following 40 mg daily of the racemate (similar trends were observed with 20 mg daily of the single enantiomer) [95], together with a faster onset of action, reduction in side effects and improved tolerability profile [95,96]. The single enantiomer is available in the UK and USA.</td>
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<tr>
<td><strong>($S$)-Ketamine</strong></td>
<td><strong>Anaesthetic</strong></td>
<td>($S$)-Ketamine has a greater analgesic and anaesthetic potency than the $R$-enantiomer in both animals and man [83,84]; post anaesthetic emergence reactions (hallucinations and agitation) are predominantly associated with the $R$-enantiomer [84,85]. The single $S$-enantiomer is available in Germany [85].</td>
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<tr>
<td><strong>Levocetirizine</strong></td>
<td><strong>H&lt;sub&gt;1&lt;/sub&gt;-Antihistamine</strong></td>
<td>$R$-Enantiomer of cetirizine; $K_i$ values against H&lt;sub&gt;1&lt;/sub&gt;-receptors 3.2 and 6.3 nM for the $R$-enantiomer and racemate respectively. Clinical studies have indicated the equivalence of a 2.5 mg dose of the single enantiomer compared to 5 mg of the racemate, the $S$-enantiomer being essentially inactive [97,98].</td>
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Cisatracurium  | Neuromuscular blocker | Developed from atracurium, a compound containing four chiral centres in its structure which due to its symmetrical nature exists as a mixture of ten stereoisomeric forms [89]; cisatracurium, the $1R,2R,1'R,2'R$-stereoisomer comprises approximately 15% of the mixture [90,91]. The single stereoisomer is approximately three fold more potent than the mixture, with a slightly slower onset of action and reduced histamine releasing properties [90,91]. As a result of the lower dose requirement of the single stereoisomer the formation of laudanosine (a metabolite reported to induce seizures in animals) is reduced compared to atracurium [91].

$(R)$-Salbutamol [levalbuterol]  | $\beta_2$-agonist | Racemic and $(S)$-salbutamol induce airway hyperresponsiveness in sensitised animals; use of the racemate is associated with some loss of bronchodilator potency, decreased protection against bronchoprovocation and increased sensitivity to allergen challenge and bronchoconstrictor stimuli [92]. Studies in humans have indicated that inhalation of $(R)$-salbutamol produces significantly greater bronchodilatation than the equivalent dose of the racemate [93]. The single enantiomer is available in the USA.

$(R,R)$-Methylphenidate  | Attention-deficit hyperactivity disorder | The $R,R$-enantiomer is approximately ten fold more potent than $(S,S)$-methylphenidate in the inhibition of dopamine and noradrenaline into striatal and hypothalamic synaptosomes respectively [99]. The drug undergoes enantioselective disposition, due to presystemic metabolism, the absolute bioavailability being ~0.23 and ~0.05 for the $R,R$- and $S,S$-enantiomers respectively [100]. Reported to be equally effective as the racemate at half-the-dose with the advantages of a more rapid-onset of action and possible improved side effect profile [101]. Available in the USA.

The activity of racemic sibutramine, a monoamine reuptake inhibitor used for the treatment of obesity, is associated with the formation of both its desmethyl and didesmethyl metabolites. Examination of the pharmacological activity of the enantiomers of the metabolites in vitro has indicated the greater potency of the $R$- compared to the $S$-enantiomers and the racemic drug, in the inhibition of noradrenaline, serotonin and dopamine uptake. Also, in vivo studies have revealed the greater anorexic potency and locomotor activity of the $R$-enantiomer metabolites in rats [40]. Interestingly, the in vivo investigations indicated that the anorexic effects could be dissociated from the locomotor activity. These observations have resulted in the suggestion that single enantiomer versions of the metabolites could provide safe and
effective treatments for both obesity and depression [40]. According to the Sepracor website (http://www.sepracor.com) one of the \(R\)-metabolites (which is not specified) is undergoing evaluation for the treatment of refractory depression, whereas an \(S\)-enantiomer metabolite (again not specified) is being evaluated for treatment of sexual dysfunction [41].

The \(R\)-enantiomer of the racemic nonsteroidal anti-inflammatory drug flurbiprofen has been evaluated in clinical trials for the treatment of late-stage prostate cancer [42]. This trial followed investigations indicating the activity of the single enantiomer in animal models of prostate (TRAMP mouse) and colon (Min mouse) cancer [43,44]. Additionally, recent evidence has indicated the potential of NSAIDs for the prevention of Alzheimer’s disease [45,46]. As \((R)\)-flurbiprofen is essentially inactive with respect to inhibition of cyclooxygenases 1 and 2, it has been suggested that it may be a useful candidate for clinical development [47] without the gastrointestinal side effects observed with the racemic drug [48,49]. An Investigational New Drug Application has recently been submitted to the US FDA, by Encore Pharmaceuticals, in order to start clinical trials with \((R)\)-flurbiprofen for the treatment and prevention of Alzheimer’s disease. In both the above examples the evaluation of the single enantiomers has the potential to provide new therapeutic indications for “old” drugs.

Such re-evaluations of single enantiomers are not without problems and examples may be cited where removal of the so-called isomeric impurity has not resulted in the supposed advantages being realised or unexpected adverse reactions have resulted. The development of the single \(\beta\)-blocking \(R\,R\)-stereoisomer, named dilevalol, of the combined \(\alpha\)- and \(\beta\)-blocking drug labetalol was terminated due to adverse effects associated with hepatotoxicity [50,51]. Sotalol is a racemic non-selective \(\beta\)-blocking agent with class III antiarrhythmic activity [52]. The \(\beta\)-blocking activity resides predominantly in the (-)-enantiomer, with (+)-sotalol being 14 to 50 fold less active depending on the test system used, whereas the enantiomers are equipotent with respect to their antiarrhythmic activity [52,53]. The (+)-enantiomer was evaluated in patients with depressed ventricular function following myocardial infarction in the SWORD trial (Survival With Oral d-Sotalol) [54]. The investigation was terminated prematurely due to increased mortality in the drug treatment group compared to the placebo control group [54]. It has been proposed that the combination of \(\beta\)-blockade and class III antiarrhythmic activity present in the racemate provides a more effective therapy than the class III antiarrhythmic activity alone [51]. More recently the development of \((R)\)-fluoxetine was terminated due to a small, but significant increase in QTc prolongation during clinical evaluation at the highest dose level examined [55,56]. The above examples indicate that the removal of the isomeric ballast present in a racemate is not a trivial matter and additionally may have considerable financial consequences (see below).

An additional point associated with these single enantiomer “failures” is that racemic mixture formulations are still available and widely used. In the present regulatory climate with respect to chiral drugs if the single enantiomers had been developed initially and “failed” during development it is highly unlikely that any major pharmaceutical company would have attempted to re-evaluate and develop the racemates. Thus, therapeutically useful agents would have been lost. Similarly it is possible that therapeutically useful compounds may have been lost as the racemates
were evaluated and thought to be unsuitable for development, whereas their individual enantiomers may have had pharmacologically useful properties.

In addition to the single enantiomer “failures” outlined above there is also an instance where following the successful launch of a single stereoisomer both it, and the original racemate, were withdrawn some years later. The anorectic agent fenfluramine was one of the first compounds to undergo the chiral switch process with the marketing of the single S-enantiomer, dexfenfluramine. Following an association of the drug with valvular heart disease, initially involving the fenfluramine-phentermine combination (the so-called fen-phen combination) in the USA [57] and the rare but serious risk of pulmonary hypertension, both the single enantiomer and racemate were voluntarily withdrawn worldwide in September 1997 [57,58].

**ECONOMIC CONSIDERATIONS**

The global market for pharmaceuticals is enormous, estimated to be worth approximately $ 300 billion US in 1997 [59]. However, over the next five years the patents on a number of drugs, the market worth of which is quoted as $ 40 billion, are due to expire [60]. There is also evidence that the rate of development of new agents is declining [60-62], for example the US FDA approved only 28 new chemical entities in 2001 which is reported to be the lowest number for 30 years [60]. The situation is compounded by the fact that research and development costs are increasing, having doubled over the last fifteen years [61], and were estimated to be between $ 300 and 400 million in 1997 [63]. The current cost estimates of bringing a drug to market are of the order of $ 600 million [60] and may be as high as $ 800 million [61]. Additionally, drug development time is now so long that the average effective patent life of a “new” agent is only 10-12 years [60].

As a number of commercially highly successful drugs are chiral the economic significance of stereochemistry to the pharmaceutical industry is obvious. The chiral switch process provides a strategy to extend the profitable life of a pharmaceutical “bestseller”; and may result in extended patent protection and provide an advantage against generic competition.

In some instances it could be argued that the development of a single stereoisomer from a racemate would not result in a significant therapeutic advantage [59]. In the case of omeprazole, the biggest selling drug worldwide in 1997, sales the USA alone being greater than $ 5 billion [59], there is some controversy regarding the relative merits of the single enantiomer [64]. The enantiomers of omeprazole, and the related proton pump inhibitors, lansoprazole and pantoprazole, have been reported to be essentially equipotent both in *in vitro* test systems and *in vivo* in the rat [64]. As these agents undergo acid catalysed transformation into an achiral cyclic sulphenamide which then covalently binds with the proton pump it is difficult to see a pharmacodynamic rationale for the development of a single enantiomer [64]. An additional complication in the case of esomeprazole/omeprazole is that a number of clinical studies compare 40 mg doses of the single enantiomer with a 20 mg dose of the racemate which makes comparison between the two agents difficult. However, as pointed out in Table 2, there are
pharmacokinetic differences between the enantiomers and some clinical studies, based on equal doses, do indicate potential therapeutic advantages of the single enantiomer [65].

There are however financial risks associated with the development of single enantiomers from racemates and it has been estimated that the research and development costs of dilevalol were $100 million [66]. Similarly the recent termination of the licensing agreement between Eli Lilly and the specialist chiral chemical company Sepracor, for the development of (R)-fluoxetine, resulted in the latter company receiving only $23 million of what was to have been a $90 million deal, additionally the stock value of Sepracor fell by 28% [56]. Such costs within the industry may be regarded as relatively modest in comparison to the cost associated with taking a novel therapeutic agent to market, particularly as by the nature of the process the possibility of success is that much greater.

CONCLUDING COMMENT

This article has attempted to provide an overview of the current situation regarding the Chiral Switches. Re-evaluation of the enantiomers of racemic drugs will undoubtedly continue and, in some instances, result in the introduction of single enantiomer versions of established drugs. Hopefully, such re-evaluations will provide agents with a “cleaner” pharmacological profile, improved safety and efficacy, and ultimately therapeutic benefits in addition to commercial advantages. Since the completion of this article a comprehensive review of the Chiral Switch, including a discussion of the patentability and intellectual property situation associated with the development of single stereoisomers from racemates has been published [41]. The attention of interested readers is also drawn to the articles by Agranat and Caner [103] concerning intellectual property and drug stereochemistry and that of Strong [104] which reviews the FDA policy on stereoisomer regulation and associated exclusivity law.

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CHIRÁLNY „SWITCH“:
VÝVOJ ČISTÝCH ENANTIOMÉROV LIEČIV Z ICH RACEMICKÝCH ZMESÍ

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V posledných desiatich až pôlnejich rokoch sa stala predmetom vážneho záujmu chiralita liečiv, hlavne porovnanie čistých enantiomérov a racemických zmesí. Pokrok v chemických technológiách spojených so syntézou, separáciou aanalyzou čistých enantiomérov z racemátov,
spolu s regulačnými opatreniami, spôsobil zvýšenie počtu nových registrovaných chirálnych liečiv vo forme čistých enantiomérov. Okrem nových chemických entit sa prehodnocuje množstvo "starých" racemátov ako potenciálne nové produkty vo forme čistých enantiomérov, ktoré by mali zlepšiť terapeutický profil. Tieto tzv. chirálne "switch" viedli k tomu, že v rovnakom čase sú na trhu dostupné liečiva vo forme racemáty i vo forme čistých enantiomérov. Avšak nie vždy sa dosiahol žiadaný terapeutický efekt a výskytli sa aj neočakávané nezadušte účinky. V článku sú zahnuté terapeutické a ekonomické problémy spojené s procesom chirálneho "switchu" liečiv.