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THERAPEUTICS INITIATIVE Evidence Based Drug Therapy

Do Single Stereoisomer Drugs Provide Value?

Stereoisomers are molecules with one or more "chiral" centres that allow the possibility of forms with the same chemical formula but differing spatial arrangements. Quinidine and quinine are a naturally occurring pair of stereoisomers, which have been developed for different therapeutic uses. Enantiomers are a type of stereoisomer in which the molecules have two non-superimposable mirror image forms. As a hand fits a glove, only the "right" or "left" handed enantiomer may fit a molecular receptor at a drug's desired site of action. A compound containing an equal proportion of each enantiomer is called a racemic mixture.

Natural compounds are often single enantiomers (e.g. levothyroxine, levodopa, l-noradrenaline). In contrast, many commercially synthesized drugs are racemic mixtures (e.g. adrenaline, warfarin, fluoxetine, omeprazole).

In principle, any of the following properties could render a single enantiomers preferable[1]:

- the single form has fewer adverse effects
- the desired action of the active form is interfered with by the inactive form
- one form is more prone to adverse drug interactions

Many familiar drugs were introduced to the market as single enantiomers, e.g. paroxetine (Paxil®) and sertraline (Zoloft®). **However, when the patent of a successful racemic drug nears expiry, it can be *remarketed* as a single enantiomer under a new patent.[2]**

Are single enantiomers better?

a) Esomeprazole (Nexium®), licensed in 2001, is the S-enantiomer of racemic S,R-omeprazole (Losec®, Prilosec® in the US).

Approved Indications: reduction of gastric acid secretion including reflux esophagitis, gastroesophageal reflux disease and in combination with

antibiotics for eradication of *H. pylori* associated with peptic ulcer disease. Alternative proton pump inhibitors (PPIs) include omeprazole, pantoprazole, lansoprazole and rabeprazole.

Pharmacokinetics: Both S- and R-omeprazole are pro-drugs, which are converted within the parietal cell to the active proton pump inhibitor, which lacks a chiral centre. Both the S- and R-forms are unstable in stomach acid, but are well absorbed when taken with water.[3,4] The duration of acid suppression is determined by irreversible inhibition of the proton pump, rather than by the parent drug's elimination half-life. **Because S-omeprazole is less susceptible to small intestinal and hepatic metabolism than the R-form, at equal doses, esomeprazole achieves 70 to 90% higher steady-state serum concentrations than racemic omeprazole.[3-5]** Therefore lower doses of esomeprazole can be used to produce equivalent acid suppression to omeprazole. Genetic differences in metabolism of the enantiomers are known, but have no clinically important impact.[6]

Evidence of efficacy: Published comparative trials of esomeprazole for gastroesophageal reflux disease and eradication of *H. pylori* used approximately 2 to 4-fold higher equivalent doses of esomeprazole than the comparator drugs.[7]

Table 1. Proton pump inhibitors: Available doses and cost.

Drug	Brand name (formulation)	Available doses (mg)	Usual daily dose range (mg)	Average daily cost*
Omeprazole	Losec® (tablet)	10, 20	10 – 40	$1.13 – 4.52^
Esomeprazole	Nexium® (tablet)	20, 40	10 – 40#	$0.55 – 2.20^
Pantoprazole	Pantoloc® (tablet)	20, 40	20 – 80	$1.02 – 4.08^
Lansoprazole	Prevacid® (capsule)	15, 30	15 – 60	$2.09 – 4.20
Rabeprazole	Pariet® (tablet)	10, 20	10 – 40	$0.70 – 2.80

Switching from omeprazole to esomeprazole at the same dose leads to a 70 to 90% increase in serum concentrations.
* Prices are based on average Pharmanet cost for 2001, or wholesale price plus 7%.
^ assumes cutting tablets to halves or quarters when possible to minimize cost.

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No trials have demonstrated an intrinsic therapeutic advantage of esomeprazole over other PPIs at equivalent doses.

Dose and cost: Esomeprazole is available in Canada as 20 and 40 mg tablets of multiple tiny enteric-coated granules (each tablet costs $2.20). Switching from other PPIs to an approximately equivalent dose of esomeprazole, has the potential to substantially reduce the daily cost to the patient (see Table 1). This may or may not require pill splitting. Pre-clinical experiments with dissolved esomeprazole and the product monograph suggest that cutting the tablets should not affect absorption, if the tablet fragment is taken with a glass of water on an empty stomach. [3,4,8] Pill splitting strategies are increasingly popular in Health Management Organizations and hospitals.[9]

Conclusion: Esomeprazole at equivalent doses offers no therapeutic advantage over other PPIs. It has a price advantage if the dose is adjusted to the approximate equivalent dose of alternative PPIs. This may require cutting the tablets and/or taking the dose every other day, when clinically appropriate.

b) Levofloxacin (Levaquin®), licensed in 1998, is the pure L-form of the racemic mixture, ofloxacin (Therapeutics Letter #26). The L-form contains the antimicrobial activity; the D-form is pharmacologically inert. Brand name racemic ofloxacin (Floxin®, same manufacturer) was similarly priced, offering no cost advantage. Generic ofloxacin is now available and less expensive at comparable doses (800 mg ofloxacin contains 400 mg levofloxacin) (see Table 2). Since once-daily levofloxacin has been proven effective, ofloxacin could be prescribed similarly.

Clinically important resistance of ***S. pneumoniae*** to levofloxacin (thus also ofloxacin) is now documented in Canada.[10]

Table 2. Available doses and prices of ofloxacin and levofloxacin

Drug	Brand name	Available doses (mg)	Usual daily dose range (mg)	Average daily cost*
Ofloxacin	Floxin®, generic	200, 300, 400	400 to 800	$1.93 - 3.86
Levofloxacin	Levaquin®	250, 500	250 to 500	$4.69 - 5.52

*Prices are based on average Pharmanet costs for 2001.

Enantiomeric drugs under development

a) S-citalopram (escitalopram): The S-enantiomer of racemic citalopram (Celexa®), is about 30-fold more potent an inhibitor at the serotonin transporter in vitro than its R-counterpart.[11] Current knowledge provides no reason to expect a clinically significant advantage over the racemate.[12] Both the antidepressant effect and adverse events (nausea, diarrhea, insomnia, dry mouth, ejaculatory disorder) were similar for S-citalopram at 10 or 20 mg/day and racemic citalopram at 40 mg/day in one 8-week DBRCT.[13]

b) R-fluoxetine: Both enantiomers of fluoxetine (Prozac®, generic) have a relatively long elimination half-life (> 2 days). The longer-lived demethylated active metabolite of S-fluoxetine is more potent than its R-desmethylfluoxetine counterpart. Interestingly, drug development of both enantiomers for different indications is underway (R-fluoxetine for depression and S-fluoxetine for migraine).[1] There is no evidence yet that either single enantiomer is preferable to racemic fluoxetine.

c) R-salbutamol (R-albuterol in the US): The active enantiomer of racemic salbutamol (Ventolin®) has been licensed in the US since 1999. Despite a significantly higher price than racemic salbutamol, it offers no demonstrated clinical advantage.[14]

Conclusions: The concept that a single enantiomer of a chiral drug may be preferable to a racemic mixture is intellectually appealing. However, in most instances this strategy has not been demonstrated to confer any clinical advantage.

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This Letter contains an assessment and synthesis of publications up to September 2002. We attempt to maintain the accuracy of the information in the Therapeutics Letter by extensive literature searches and verification by both the authors and the editorial board. In addition this Therapeutics Letter was submitted for review to 50 experts and primary care physicians in order to correct any inaccuracies and to ensure that the information is concise and relevant to clinicians.