EFFECT OF ALOSETRON AND TEGASEROD AT THE 5-HT$_{2B}$ RECEPTOR IN HUMAN COLON

R. Borman, J. Wade, J. Root, D. Riddy, K. Clark, R.A. Coleman
Pharmagene Laboratories Ltd, Orchard Road, Royston, SG8 5HD, UK

1. Introduction

Alosetron, a 5-HT$_3$ receptor antagonist, and tegaserod, a 5-HT$_4$ receptor partial agonist, are both reported to show some efficacy in the treatment of irritable bowel syndrome (IBS). Tegaserod has also previously been reported to show high affinity for 5-HT$_{2B}$ receptors (Beattie *et al*., 2004, *Br. J. Pharmacol.,* 143, 549). Activation of 5-HT$_{2B}$ receptors has previously been shown to induce excitatory effects in human colon smooth muscle *in vitro* (see Figure 1), and it has been suggested that these excitatory effects may be responsible for some of the symptoms of IBS (Borman *et al., Br. J. Pharmacol.,* **135,** *1144-1151)*. The aim of the present study was to investigate the pharmacology of both tegaserod and alosetron at human 5-HT$_{2B}$ receptors, both expressed in a cell line and in native form in human colon.

2. Methods

All samples of colon were obtained through medically qualified intermediaries with the informed consent of the donor, and with approval of the local ethics committee. Longitudinal muscle strips of human colon were mounted in organ baths, where they were electrically stimulated to induce neurally-mediated contractions. The ability of the selective 5-HT$_2$ receptor agonist α-Me-5-HT to potentiate these contractions was then determined in the absence and presence of alosetron or tegaserod, in order to determine the ability of the compounds to block native human 5-HT$_{2B}$ receptors. In parallel, the ability of the compounds to bind to human recombinant 5-HT$_{2B}$ receptors expressed in CHO-K1 cells was determined using standard radioligand binding techniques.

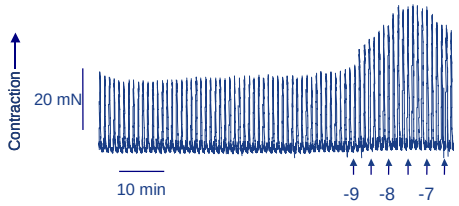

Figure 1. Effect of 5-HT on electrically-induced contractions in human colon smooth muscle. 5-HT causes potentiation of neurally-mediated contractions.

3. Results

In radioligand binding studies, both alosetron and tegaserod showed high affinity for human recombinant 5-HT$_{2B}$ receptors, with pK$_i$ values of 7.0±0.4 and 8.6±0.5 respectively (mean±s.e.mean, n=4). In human colon, both compounds blocked the effects of α-Me-5-HT, with pA$_2$ values of 7.8±0.1 and 6.9±0.2 respectively (mean±s.e.mean, n=3-4, Table 1). Thus in human colon, the potency of tegaserod was less than would be expected from binding data (see Table 1 and Figure 2a), whereas the effect of alosetron was greater (Table 1 and Figure 2b).

Compound	5-HT$_{2B}$ binding pK$_i$	5-HT$_{2B}$ colon pA$_2$
Tegaserod	8.6±0.5	6.9±0.2
Alosetron	7.0±0.4	7.8±0.1

Table 1. Affinity of tegaserod and alosetron at human recombinant 5-HT$_{2B}$ receptors and antagonist potency at the 5-HT$_{2B}$ receptor in human colon. Data are given as mean±s.e.mean for n=3-4 determinations). Both compounds have affinity at, and are antagonists of, human 5-HT$_{2B}$ receptors

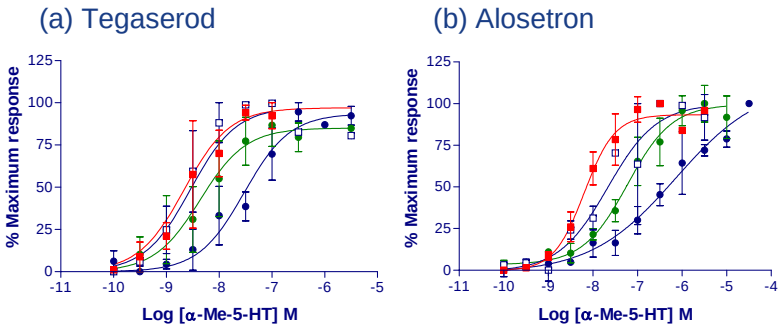

Figure 2. Effect of increasing concentrations of (a) tegaserod and (b) alosetron on the response to α-Me-5-HT in human colon smooth muscle. Data are shown as response to α-Me-5-HT in the absence (■) and presence of antagonists at 10^{-8}M (□), 10^{-7}M (●) and 10^{-6}M (●), and are given as mean±s.e.mean for n=3-4 donors. Tegaserod and alosetron antagonise the 5-HT$_{2B}$-mediated excitatory effects in human colon

4. Summary

Both alosetron and tegaserod have shown clinical efficacy at reducing certain symptoms of IBS, including pain, and it has previously been shown that tegaserod at least, displays some affinity for 5-HT$_{2B}$ receptors. In the present study, we have confirmed the affinity of tegaserod for human 5-HT$_{2B}$ receptors, but have shown that the compound blocks 5-HT$_{2B}$ receptors in human colon with lower potency than anticipated. In addition, we have shown that alosetron also displays affinity for, and antagonism of, human 5-HT$_{2B}$ receptors in both a cell line and in human colon. It remains to be demonstrated whether the clinical efficacy of these two compounds in IBS patients is due to blockade of 5-HT$_{2B}$ receptors, and whether a more potent and selective 5-HT$_{2B}$ receptor antagonist may prove more efficacious in the clinic.

PHARMAGENE®
Human Intelligence