THE ACUTE AND CHRONIC EFFECTS OF H₁ RECEPTOR BLOCKADE WITH ASTEMIZOLE ON INDOCYANINE GREEN CLEARANCE

D.N. BATEMAN, P.H. CHAPMAN & M.D. RAWLINS

Wolfson Unit of Clinical Pharmacology, University of Newcastle upon Tyne, Newcastle upon Tyne NE1 7RU

- 1 The effects of acute and chronic (3 months) dosing with astemizole on indocyanine green kinetics have been investigated in normal volunteers and patients.
- 2 A single dose of astemizole 40 mg produced significant reduction in indocyanine green clearance ($P < 0.02$) and volume of distribution ($P < 0.02$) when assessed at 48 h, but not at 24 h.
- 3 In six volunteers who did not receive astemizole there was no significant change in indocyanine green kinetics over a 48 h period.
- 4 In seven patients on chronic treatment with astemizole there was no significant change in indocyanine green kinetics when these were measured at 1 month and 3 months and compared to pre-treatment values.
- 5 The change in indocyanine green clearance and volume of distribution following acute astemizole treatment did not correlate with H₁-receptor antagonism.
- 6 Change in indocyanine green clearance following acute drug administration may not be due to changes in liver blood flow and should therefore be interpreted with caution.

Keywords astemizole indocyanine green H₁-receptor blockade

Introduction

Interest in the effects of histamine receptor blockers on liver blood flow in man has arisen as a result of the demonstration that indocyanine green clearance, an indirect measure of liver blood flow, is altered by acute treatment with the H₁-receptor antagonist chlorpheniramine (Feely & Wood, 1982). The implications of this observation, however, are unclear: first, the reliability of indocyanine green as an index of liver blood flow, especially after repeated administration, has been challenged (Grainger *et al.*, 1982; Jackson, 1981; Lebrech *et al.*, 1981); secondly, chlorpheniramine possesses other pharmacological properties in addition to its antihistamine ones (Douglas, 1980); thirdly, if H₁-antagonists do have effects on liver blood flow, this might have important clinical implications both for the treatment of patients with liver disease, and for the hepatic clearance of drugs with a high extraction rate above the liver. We have therefore examined the effects of single and multiple doses of astemizole on indocyanine green clearance.

Methods

Patients and volunteers

Indocyanine green clearance was measured in seven patients receiving astemizole for the treatment of chronic urticaria or severe pruritis, and in whom there was no biochemical evidence of hepatic dysfunction. These patients received 10 mg astemizole daily and were part of a larger group of patients who have been reported separately in terms of the effects of astemizole on histamine induced weal and flare (Bateman *et al.*, 1983). Indocyanine green clearance was measured before starting therapy, and after 1 and 3 months continuous administration.

Nine healthy drug-free male volunteers (aged 22 ± 0.2 years) were given a single dose of astemizole (40 mg) and indocyanine green clearance measurements were made at 0, 24 and 48 h. Six healthy male volunteers (aged 31 ± 2.5 years) acted as controls and underwent measurement of indocyanine green clearance at the same times.

Indocyanine green clearance

Patients and volunteers attended the laboratory having fasted from midnight. They rested supine for 30 min before the administration of indocyanine green (0.5 mg kg^{-1} body weight). Blood samples were withdrawn every 3 min for 21 min from the contra-lateral arm to that used for administration of indocyanine green. Indocyanine green concentrations were assayed in plasma following centrifugation using a standard indocyanine green calibration curve prepared from the patient's own plasma withdrawn before the administration of the dye (Caesar *et al.*, 1961). In our hands the lower limit of sensitivity of the assay was 0.2 mg/l . Plasma clearance was calculated assuming a mono-exponential decline as previously described (Caesar *et al.*, 1961; Daneshmend *et al.*, 1981). Whole blood clearance of indocyanine green was calculated from the plasma clearance and the measured haematocrit on each occasion (Caesar *et al.*, 1961).

Histamine antagonism

Histamine antagonism was assessed by measuring the inhibition of weal and flare reactions to intradermal injection of 2, 20 and 60 mg of histamine acid phosphate (as histamine base) in 0.1 ml of 9% w/v sodium chloride solution in the flexor aspect of the forearm. Histamine antagonism to both weal and flare was derived from the area under the histamine dose-response curve as previously described (Bateman *et al.*, 1983).

Results

Single dose studies

The whole blood clearance of indocyanine green in subjects who did not receive astemizole (1–6, Table 1) was not significantly altered at 24 or 48 h, when compared to time 0. In the subjects who received 40 mg of astemizole (subjects 7–15, Table 1) apparent liver blood flow before astemizole administration was $1.42 \pm 0.11 \text{ l/min}$ and fell to $1.30 \pm 0.096 \text{ l/min}$, ($P < 0.2$) at 24 h and to $1.13 \pm 0.076 \text{ l/min}$, ($P < 0.02$) at 48 h.

In the controls (Table 1) indocyanine green volume of distribution did not change significantly over the 3 days, but in the astemizole group there was a significant reduction ($P < 0.02$) by 48 h (3.65 l to 2.79 l). The plasma half-life of indocyanine green in the controls was similar at 0 and 48 h ($3.44 \pm 0.24 \text{ min}$ and $3.43 \pm 0.29 \text{ min}$ respectively). In the treated group there was a reduction in half-life by 48 h ($3.12 \pm 0.16 \text{ min}$ to $2.87 \pm 0.13 \text{ min}$) but this was not statistically significant ($P > 0.3$). The response to intradermal

histamine after astemizole was 35% (weal) and 56% (flare) of control at 24 h. By 48 h, these were 25% and 29% respectively. There was no correlation between the suppression of the histamine weal or flare and the change in apparent liver blood flow or volume of distribution of indocyanine green.

Chronic dosing

Patients undergoing chronic administration with astemizole showed no significant change in either whole blood clearance or apparent volume of distribution (Table 2) over 3 months. Half-life was also similar before treatment, and after 3 months ($3.29 \pm 0.43 \text{ min}$ and $3.23 \pm 0.34 \text{ min}$ respectively).

The response to intradermal histamine at 3 months, was 12.4% (weal) and 24.4% (flare) of pre-treatment response.

Discussion

The whole blood clearance of indocyanine green has been widely used as an estimation of apparent liver blood flow. In our controls the method was found to be reproducible with a coefficient of variation of approximately 5%. This variation, and the values obtained for apparent liver blood flow, are similar to those reported by Daneshmend *et al.* (1981).

Forty-eight hours after a single dose of astemizole (40 mg) the change in indocyanine green clearance was similar in magnitude to the change reported by Feely & Wood (1982) following treatment with chlorpheniramine (8 mg three times a day for 1 day) or cimetidine (600 mg). By contrast, the controls showed there was no significant change in indocyanine green clearance over a 48 h period. The acute change in indocyanine green clearance we have observed is therefore likely to be an effect of astemizole. However, the clearance of indocyanine green depends on both liver blood flow and its hepatic extraction ratio (Jackson, 1981). It is therefore possible that the acute change in indocyanine green clearance that was observed after astemizole, does not in fact reflect a change in liver blood flow but is due to a change in the uptake of indocyanine green into the liver. It may therefore be relevant that acute treatment with astemizole produced a reduction in the apparent volume of distribution of indocyanine green of about 24% which could not be explained by a change in plasma volume, since there was no significant change in the haematocrit. An action of astemizole on binding proteins that are involved in the distribution of indocyanine green, and in the uptake of compound into the liver, would produce both a fall in clearance and indocyanine green and a decreased apparent volume of distribution. The change in indocyanine green clearance (20%) is of a similar order of

Table 1 Indocyanine green kinetics in normal subjects measured pretreatment and at 24 and 48 h with and without treatment with astemizole (40 mg)

<i>Controls</i>	<i>Whole blood clearance (l/min)</i>			<i>Apparent volume of distribution of indocyanine green (l)</i>		
	<i>0 h</i>	<i>24 h</i>	<i>48 h</i>	<i>0 h</i>	<i>24 h</i>	<i>48 h</i>
1	1.35	1.15	1.26	4.23	4.48	4.75
2	1.12	1.17	1.15	2.40	2.63	2.65
3	0.77	0.91	0.79	2.58	2.61	2.75
4	0.72	0.72	0.76	2.01	1.88	2.04
5	1.81	1.73	1.73	4.82	4.13	5.11
6	1.48	1.56	1.47	3.96	2.85	3.04
Mean	1.21	1.21	1.19	3.33	3.10	3.39
s.e. mean	0.17	0.16	0.16	0.47	0.41	0.51
<i>Subjects receiving astemizole (40 mg)</i>						
7	1.22	1.21	1.29	3.58	3.63	2.62
8	1.72	1.13	1.12	3.90	3.32	2.73
9	1.26	1.28	0.91	4.06	2.55	2.29
10	1.23	1.61	1.21	3.49	4.61	3.17
11	2.05	1.82	1.41	4.82	4.58	4.05
12	1.23	1.02	1.07	3.05	2.69	3.12
13	1.02	0.99	0.90	2.43	2.28	2.35
14	1.55	1.44	1.47	3.39	3.75	2.97
15	1.49	1.10	0.83	4.13	2.87	1.77
Mean	1.42	1.30	1.13*	3.65	3.36	2.79
s.e. mean	0.11	0.10	0.08	0.23	0.28	0.22

* $P < 0.02$ from pre-treatment**Table 2** Effects of chronic dosing with astemizole on indocyanine green kinetics in patients studied pretreatment (0) and at 1 and 3 months

<i>Patient</i>	<i>Whole blood clearance (l/min)</i>			<i>Apparent volume of distribution (l)</i>		
	<i>0</i>	<i>1 month</i>	<i>3 months</i>	<i>0</i>	<i>1 month</i>	<i>3 months</i>
3	1.06	1.70	1.38	3.06	5.21	3.64
4	0.75	1.04	1.36	1.51	1.81	2.74
5	1.09	1.21	1.01	4.67	4.39	4.01
6	1.42	1.22	1.72	4.42	4.03	4.70
9	0.85	1.04	0.97	3.44	4.47	3.62
10	1.19	1.00	1.07	3.21	1.65	2.66
11	1.08	1.07	1.36	2.27	2.30	2.66
Mean	1.06	1.18	1.27	3.23	3.41	3.43
s.e. mean	0.08	0.09	0.10	0.42	0.55	0.30

magnitude as the change in the volume of distribution and there was a weak correlation ($r = 0.56$) between the change in volume distribution of indocyanine green and the change in the indocyanine green clearance produced by astemizole. There was no correlation, as measured by changes in histamine induced weals, however, between the histamine receptor antagonism produced by astemizole and changes in the indocyanine green clearance or volume of distribution. The mechanism of the acute change in indocyanine green kinetics does not therefore appear to involve H_1 -receptor antagonism. In addition these data throw doubt on the hypothesis that H_1 -receptors are induced in the control of liver blood flow.

After chronic dosing astemizole produced no significant change in either indocyanine green clearance, volume of distribution or half-life. Feely *et al.* (1981) reported that treatment with cimetidine for 7 days produced a significant fall in apparent liver blood flow as measured by propranolol clearance, but the effect of chronic treatment with standard H_1 -receptor antagonists on liver blood flow does not appear to have been studied. The fact that acute doses of 40 mg

of astemizole produced changes in indocyanine clearance whereas chronic treatment with lower doses did not, might suggest that the absolute dose of astemizole was important in the observed effects. Astemizole however has an extremely long half-life and it is likely that the plasma concentrations of astemizole in patients on chronic treatment would be at least as high as those occurring after a single 40 mg dose (Janssen Pharmaceuticals, personal communication).

These data therefore demonstrate that chronic dosing with astemizole does not produce changes in apparent liver blood flow as measured by indocyanine green clearance. The acute effects on indocyanine green clearance may well not relate to change in liver blood flow but be due to changes in the disposition of indocyanine green which is transient. We have no explanation, however, as to the precise nature of such changes. The effects of acute drug administration on indocyanine green clearance should be interpreted with caution, since from these data it is clear that extrapolation of the effects of acute studies to the effects after chronic administration are not justified.

References

- BATEMAN, D.N., CHAPMAN, P.H. & RAWLINS, M.D. (1983). The effects of astemizole on histamine induced weal and flare.
- CAESAR, J., SHALDON, S., CHIANDUSSI, L., GUEVARA, L. & SHERLOCK, S. (1961). The use of indocyanine green in the assessment of hepatic blood flow as a test of hepatic function. *Clin. Sci.*, **21**, 45–57.
- DANESHMEND, T.K., JACKSON, L. & ROBERTS, C.J.C. (1981). Physiological and pharmacological variability in estimated hepatic blood flow in man. *Br. J. clin. Pharmacol.*, **11**, 491–496.
- DOUGLAS, W.W. (1980). In *The Pharmacological Basis of Therapeutics*, eds Gilman, A.G., Goodman, L.S. & Gilman, A. New York: Macmillan Press.
- FEELY, J., WILKINSON, G.R. & WOOD, A.J.J. (1981). Reduction of liver blood flow and propranolol metabolism by cimetidine. *New Engl. J. Med.*, **304**, 692–695.
- FEELY, J. & WOOD, A.J.J. (1982). Reduction in apparent liver blood flow in man by histamine receptor blockers and inhibition of prostaglandin synthesis. *Br. J. clin. Pharmacol.*, **13**, 592–593P.
- GRAINGER, S.L., MARIGOLD, J.H. & KEELING, P.W.N. (1982). Ranitidine and liver blood flow. *Lancet*, **i**, 398.
- JACKSON, J.E. (1981). Reduction of liver blood flow by cimetidine. *New Engl. J. Med.* **305**, 99–100.
- LEBREC, D., GOLDFARB, G. & BERHAMOU, J.P. (1981). Reduction of liver blood flow by cimetidine. *New Engl. J. Med.*, **305**, 100.

(Received March 4, 1983,
accepted May 17, 1983)