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The effect of repeated oral doses of azelastine hydrochloride on antipyrine half-life in normal volunteers

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Abstract—Treatment with azelastine 4·4 mg twice daily for 21 days did not produce any change in salivary antipyrine elimination in 8 normal volunteers.

Azelastine, 4-*p*-chlorobenzyl-2-(hexahydro-1-methyl-1*H*-azepin-4-yl)-1(2*H*)-phthalazinone hydrochloride, is a recently introduced compound which markedly inhibits allergen-induced airways obstruction in man (Ollier et al 1986) and reduces the symptoms of allergic rhinitis (Perhach et al 1984). Because it may be taken prophylactically for long periods it was desirable to investigate the possible effect of its chronic administration on hepatic drug metabolizing enzymes, using antipyrine elimination as a measure of their activity.

Subjects and methods

Fourteen healthy Caucasian subjects (9 female), aged 22–28 years, participated in the study after giving consent to the protocol which had been approved by the local ethics committee. The study was double blind. Subjects were randomly assigned to take placebo (4 subjects, 1 smoker) or azelastine 4·4 mg (10 subjects, 3 smokers) twice daily for 31 days. No abnormality of renal or liver function was found in a routine biochemical screen on the subjects before the study.

Antipyrine half-life was measured before and on the day after azelastine treatment. Antipyrine capsules 1200 mg were given orally with 50 mL water at 0800 h, and salivary collections were made at 3, 6, 9, 12, 15, 24, 28 and 33 h after dosing. Subjects were not allowed any ethanolic drinks for 24 h before or 48 h after antipyrine dosing.

Antipyrine concentrations in the saliva samples were measured by gas chromatography (Lindgren et al 1974). The assay sensitivity was 1 mg L^{-1}, intra-assay coefficient of variation $< 5\%$ and inter-assay coefficient of variation $< 7\%$. Preliminary studies had shown that azelastine did not interfere with the antipyrine estimation.

The elimination half-life was calculated by linear regression analysis of log plasma concentration against time. Area under the curve was calculated by the trapezoidal rule. The Mann Whitney (Wilcoxon) U-test was used for comparison of the two treatment groups.

Results

Two azelastine-treated subjects withdrew from the study on days 5 and 14, respectively (see below), and therefore only 8 subjects completed azelastine treatment and had their second antipyrine tests. Table 1 shows that the mean values for antipyrine half-life and area under curve were not statistically different after treatment with azelastine or placebo when compared with those before treatment. Examination of individual subject data showed no clear difference in values between smokers and non-smokers, and no relationship was apparent between degree of smoking and antipyrine half-life values.

Table 1. Group mean ± standard deviation, medians and ranges of antipyrine half-life, and area under curve values before and after treatment with azelastine or placebo for 21 days.

	Azelastine (n = 8)		Placebo (n = 4)	
Half-life (h)	Before	After	Before	After
$\bar{x} \pm$ s.d.	11·1 ± 2·6	10·2 ± 2·0	12·9 ± 3·4	11·6 ± 0·6
Median	10·2	10·2	12·5	11·6
Range	7·3–15·7	7·3–12·6	10·0–16·8	10·9–12·2
Area under curve (mg L^{-1}.h)				
$\bar{x} \pm$ s.d.	457 ± 186	384 ± 138	411 ± 122	403 ± 135
Median	416	396	399	363
Range	205–700	164–554	287–559	299–591

Adverse effects. No serious adverse drug reactions occurred. Eight subjects on azelastine and one on placebo complained of drowsiness. One subject on azelastine withdrew on day 5 because of drowsiness. A second withdrew on day 14 for reasons unrelated to the drug. No abnormalities in routine blood and urine haematological and biochemical tests were found after treatment with azelastine.

Discussion

Antipyrine elimination is the most commonly used marker of hepatic enzyme inducing activity (Mucklow 1982). The pretreatment control values for antipyrine half-life in this study were similar to those obtained in other studies of salivary antipyrine elmination in larger numbers of normal subjects (Fraser et al 1976; Stevenson 1977). We have shown that twice-daily treatment for 21 days with an oral therapeutic dose of azelastine did not produce any significant change in antipyrine half-life or in its area under the plasma concentration-time curve. It is unlikely, therefore, that long term treatment with azelastine will produce any marked change in hepatic enzyme activity, or be associated with drug interactions involving such a mechanism.

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