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Effect of anti-inflammatory drugs on partitioning characteristics of propranolol and oxprenolol

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The influence of a range of nine anti-inflammatory drugs on the octan-1-ol aqueous phosphate buffer pH 7·4 apparent partition coefficients of propranolol and oxprenolol has been examined. All produced a change in the apparent partition coefficient which can be explained in terms of partitioning of hydrophobic ion-pairs formed between the ionic anti-inflammatory compound and the protonated cationic drug.

Extensive research into the mechanism of drug absorption has shown that it proceeds mainly by the passive transfer of unionized molecules (Schanker et al 1958). However, interest has centred upon the possibility of the intervention of hydrophobic ion-pairs in the absorption process, most research being directed towards the enhancement of absorption of poorly bioavailable drugs such as quaternary bases, by the oral route (Irwin et al 1969; Kakemi et al 1969; Gibaldi & Grundhofer 1973; Masaki et al 1973; Walking et al 1978); Bhuta et al 1980). A wide variety of counter-ions have been used in these studies including inorganic ions and both endogenous and non-endogenous organic molecules including salicylate. The objective of this investigation is to assess the relative effectiveness of various acidic non-steroidal anti-inflammatory drugs (NSAIDs) in modifying the partitioning characteristics of basic drugs. This would enable an assessment to be made as to which of the acidic NSAIDs are worthy of investigation as counter-ions to modify absorptive and distributive processes. Propranolol and oxprenolol were selected as representative highly ionized organic bases for these studies.

Materials and methods

Compounds used. Propranolol hydrochloride (ICI), oxprenolol hydrochloride and phenylbutazone (CIBA), fenoproen calcium (Lilly), indomethacin and diflunisal (Merck Sharp and Dohme), naproxen (Syntex), sulindac (C E Frost Ltd), ibuprofen (Boots) and salicylic acid and oxyphenbutazone were used in the present study.

Partition experiments. Octan-1-ol was purified by washing with 1 M hydrochloric acid, 1 M sodium hydroxide, distilled water and 0·067 M phosphate buffer pH 7·4. The 0·067 phosphate buffer pH 7·4 used in the partitioning experiments was presaturated with octan-1-ol. Solutions of anti-inflammatory drugs (2×10^{-3} M) were prepared in methanol, (Unichrom HPLC grade, Ajax chemicals), the fenoprofen calcium being corrected to give the equivalent molar concentration of free acid.

To a 25 ml glass vial with screw cap was added 0·5 ml or 2·5 ml of a methanolic solution of acidic NSAID (equivalent to 1·0 and 5·0 μmol of drug respectively) and the solutions evaporated to dryness under a stream of nitrogen at 50 °C. To the tared vial was added 2·0 ml of octan-1-ol and the volume determined by weight (wt ml^{-1} 0·8332) and 20 ml of propranolol or oxprenolol solution ($2{\cdot}5 \times 10^{-5}$ M) in phosphate buffer 0·067 M pH 7·4 (equivalent to 0·5 μmol of drug). The vials were equilibrated by gentle agitation at 37 °C for 24 h, the octan-1-ol removed by aspiration and the aqueous phase submitted to hplc. Each experiment was performed in duplicate and the concentration of drug in the organic phase was deduced by subtraction and the apparent partition coefficients (K o/w (app.)) calculated.

Analytical methods. A liquid chromatograph (Pye Unicam LC3-XP) equipped with variable wavelength detector and 50 μl loop injector (Rheodyne 7125) was used. The stationary phase was octadecyl silica (Waters Assoc.) (30 cm × 6·4 mm i.d., 10 μm particle size) and the mobile phase 5×10^{-3} M heptane sulphonic acid and 0·5% acetic acid in 60% methanol for propranolol and 55% methanol for oxprenolol. Flow rate was 1.5 ml min^{-1} and the eluate was monitored at 290 nm for propranolol and 273 nm for oxprenolol.

The drugs were quantitated by the peak-height method against a calibration curve prepared from standard solutions. No internal standard was employed,

Table 1. Values of apparent partition coefficient for propranolol in the presence of acidic anti-inflammatory drugs.

Drug	1·0 μmol	(% shift)	5·0 μmol	(% shift)
Salicylic acid	29·3	(−1)*	28·7	(−4)*
Naproxen	31·6	(4)	38·7	(30)
Oxyphenbutazone	33·1	(11)	43·2	(45)
Sulindac	33·4	(12)	46·1	(55)
Fenoprofen calcium	32·8	(10)	48·2	(62)
Ibuprofen	34·9	(17)	58·6	(97)
Phenylbutazone	37·8	(27)	68·2	(129)
Indomethacin	41·3	(39)	82·9	(179)
Diflunisal	52·8	(78)	315·4	(355)

The apparent partition coefficient for propranolol in the absence of anti-inflammatory drug was 29·7.
* Salicylic acid gave a small negative shift.

the loop injector giving a coefficient of variation of 0·8% from eight replicate injections.

Results and discussion

The results of partitioning experiments for propranolol and oxprenolol in the presence of nine representative acidic NSAIDs and appropriate blank controls are listed in Tables 1 and 2 respectively.

The values obtained for the K o/w (app.) for propranolol (29·7) and oxprenolol (4·31) in the absence of NSAIDs are in agreement with previously reported values (Hellenbrecht et al 1973; Wang & Lien 1980; Woods & Robinson 1981; Schurmann & Turner 1978). The change in K o/w (app.) with increasing amounts of acidic NSAID must be associated with the formation of ion-pairs between the anion of the NSAID and the protonated species of the basic drug in the octan-1-ol phase. The possibility that the observed results arise from salting-out effects can be discounted by the high electrolyte concentration relative to the amount of acidic NSAID in the system.

As has been found in previous studies (Irwin et al 1969), a linear relationship exists between K o/w (app.) and the amount of counter-ion present in the partitioning experiment. The most effective acidic NSAID at modifying partitioning characteristics is diflunisal which, at a ten fold excess of NSAID results in an increase of 400 and 350% in the K o/w (app.) for propranolol and oxprenolol respectively. The least effective is salicylic acid which, while producing a small increase in K o/w (app.) for oxprenolol, actually reduces the K o/w (app.) of propranolol. Reduction of K o/w (app.) of propranolol in the presence of the acidic drugs hydrochlorothiazide and frusemide has been reported previously (Al-Janabi et al 1981). The ability to influence the K o/w (app.) is presumably a function of the chemical nature of the particular NSAID as reflected in its hydrophobicity and degree of ionization at pH 7·4.

The results of these experiments indicate that the acidic NSAIDs are all capable of forming ion-pairs which can significantly modify the partitioning characteristics of ionized basic drugs. Consideration should therefore be given to compounds such as diflunisal, indomethacin and phenylbutazone as modifiers of absorption and distribution phenomena as all would appear to be more effective than the previously studied salicylate (Gibaldi & Grundhofer 1973).

Table 2. Values of apparent partition coefficients for oxprenolol in the presence of acidic anti-inflammatory drugs.

Drug	1·0 μmol	(% shift)	5·0 μmol	(% shift)
Salicylic acid	4·34	(1)	4·55	(5)
Naproxen	4·60	(7)	5·56	(29)
Oxyphenbutazone	—*		—*	
Sulindac	4·75	(10)	6·10	(42)
Fenoprofen calcium	4·96	(15)	7·66	(78)
Ibuprofen	4·90	(14)	7·81	(82)
Phenylbutazone	6·30	(46)	13·60	(215)
Indomethacin	5·74	(33)	10·79	(150)
Diflunisal	7·56	(75)	21·6	(401)

The apparent partition coefficient for oxprenolol in the absence of anti-inflammatory drug was 4·31.

* Oxyphenbutazone and oxprenolol peaks overlap making determination impossible.

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