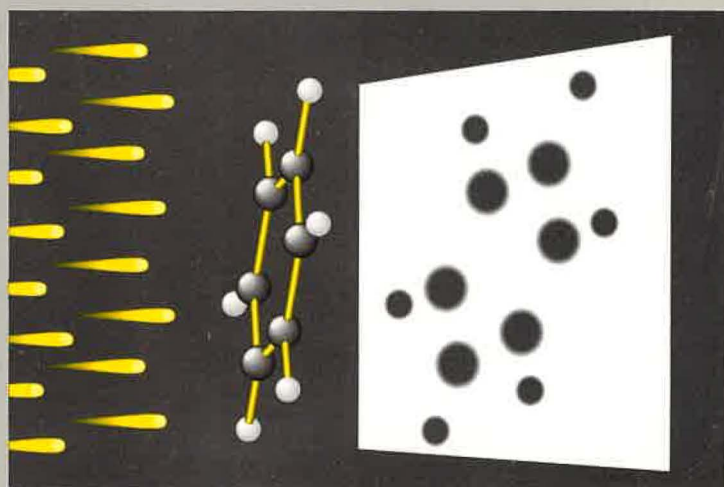


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Ketobemidone prodrugs for buccal delivery

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Various carboxylic acid and carbonate esters of the opioid analgesic ketobemidone were prepared and assessed as potential prodrugs with the aim of obtaining a ketobemidone formulation suitable for buccal or sublingual absorption. The chemical stability, enzymatic hydrolysis and lipophilicity characteristics of the esters were studied using HPLC assay procedures. All esters were rapidly hydrolyzed in human plasma, the half-lives ranging between 0.03 and 1.8 min. A marked enzymatic hydrolysis took place in whole human saliva, the half-lives of hydrolysis being in the range 3-295 min. All esters were more lipophilic than the parent ketobemidone, as determined by octanol-buffer partition experiments and by reversed-phase column chromatography. The relatively high resistance of the sterically hindered 3,3-dimethylbutyryl ester to undergo hydrolysis in saliva combined with its facile plasma-enzyme catalyzed conversion and high lipophilicity makes this ester the most promising prodrug candidate for buccal delivery.

Ketobemidone, 1-[4-(3-hydroxyphenyl)-1-methyl-4-piperidyl]-1-propanone (I), is a strong narcotic analgesic which has been used clinically for more than forty years, especially in Scandinavia and in some other European countries. The drug is usually administered perorally or rectally but its bioavailability is incomplete and variable. The mean bioavailabilities in human have been reported to be 34 and 44% following peroral and rectal administration, respectively [1, 2].

By buccal or sublingual dosing, the bioavailability can often be substantially improved because when administered by these routes the drug is not exposed to the metabolic enzymes of the intestines and liver during absorption. Furthermore, these routes offer the potential for more rapid absorption and onset of action relative to the peroral and rectal routes. Recent studies have shown that the bioavailability of various opioid analgesics can be greatly improved by buccal or sublingual administration [3-6].

The purpose of the present study was to develop a ketobemidone preparation suitable for buccal or sublingual administration in order to improve its bioavailability and achieve a more rapid onset of action relative to the peroral preparation. Initial studies using the *in vivo* buccal absorption model by Beckett and Triggs [7] showed, however, that ketobemidone did not penetrate the oral mucosa. This can most likely be ascribed to the limited lipophilicity of the compound. This physico-chemical property is known to be an important parameter in the penetration of drugs across the oral mucosal barrier [6, 8-12]. A promising approach to improve the buccal absorption of ketobemidone may be the development of more lipophilic prodrugs which are converted back to the active parent drug during or after absorption. In this paper, the synthesis of various carboxylic acid and carbonate esters (II-XI) of ketobemidone is described, along with data on the chemical stability, enzymatic hydrolysis and lipophilicity of the esters.

Experimental

Apparatus

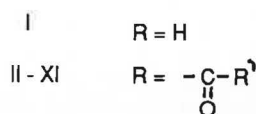
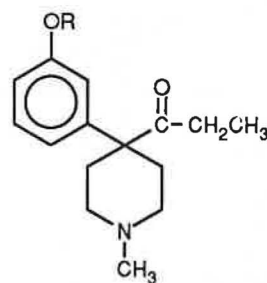
Measurements of pH were performed at the temperature of study using a Metrohn, type 632, pH Meter instrument. High-performance liquid chromatography (HPLC) was carried out using a system consisting of a Milton Roy constaMetric 3000 pump, a variable-wavelength UV-detector type Milton Roy spectroMonitor 3100 and a Rheodyne 7125 injection valve with a 20 µl loop. A deactivated reversed-phase Supelcosil LC-8-DB column (33 × 4.6 mm) (3-µm particles) equipped with a Supelguard 20 mm precolumn (both from Supelco Inc. U.S.A.) was used. Elemental analyses were performed at Leo Pharmaceuticals, Ballerup, Denmark.

Chemicals

Ketobemidone hydrochloride was obtained from H. Lundbeck A/S, Copenhagen, Denmark. Buffer substances and solvents used were of reagent grade.

Synthesis of ketobemidone esters

The carboxylic acid and carbonate esters (II-XI) of ketobemidone were prepared by reacting ketobemidone with the



* Correspondence

appropriate acid chloride or chloroformate in a two-phase system comprising aqueous bicarbonate solution and methylene chloride. This method was adapted from a previously described analytical derivatization technique for ketobemidone [13, 14]. The method can be illustrated with the preparation of the pivaloyl ester III: Pivaloyl chloride (20 mmol, 2.46 ml) was added to a stirred mixture of ketobemidone hydrochloride (4 mmol, 1.12 g), 40 ml of a 0.5 M aqueous solution of sodium bicarbonate (pH 9.6) and 40 ml of methylene chloride. The mixture was stirred at room temperature for 3 h whereupon the layers were separated. The organic phase was washed with water, dried over anhydrous sodium sulfate and evaporated under reduced pressure to give pivaloyl ketobemidone as an oil. The oil was dissolved in ether (50 ml) and a 2.5 M methanolic hydrochloric acid solution (5 mmol, 2 ml) was added. After standing overnight at -20°C the precipitated hydrochloric acid salt of III was filtered off and recrystallized from acetone-ether. The yield was 68%.

In the case of the 3,3-dimethylbutyrylester IV, a fumarate salt was prepared. This was done by adding a solution of fumaric acid in 2-propanol to a solution of the base form of the ester in ether.

All compounds showed elemental analysis (C, H and N) within $\pm 0.4\%$ of the theoretical values. Physical and analytical data for the esters are given in Table 1.

Analysis of ketobemidone and its esters by HPLC

A reversed-phase HPLC procedure was used for the quantitative determination of ketobemidone esters and the parent drug. A deactivated Supelcosil column was eluted with a mixture of methanol-acetonitrile-0.1% phosphoric acid containing triethylamine (10^{-3} M) in order to improve peak shape. For the analysis of ketobemidone, the composition of the mixture was 5:15:80 (v/v) whereas for the esters the amount of methanol was 5% v/v and that of acetonitrile between 15 and 40% v/v in order to provide an appropriate retention time. The flow rate was $1-2\text{ ml min}^{-1}$ and the column effluent was monitored at 215 or 280 nm. Quantitation of the compounds was done by measurement of peak heights in relation to those of standards chromatographed under the same conditions.

Kinetic measurements

Hydrolysis kinetics in aqueous solutions. The hydrolysis of the ketobemidone derivatives was studied in aqueous buffer solutions at $60.0 \pm 0.2^{\circ}\text{C}$ and, in some cases, at $37.0 \pm 0.2^{\circ}\text{C}$. Hydrochloric acid, acetate, phosphate, borate, carbonate and

sodium hydroxide solutions were used as buffers; the total buffer concentration was 0.02 M. A constant ionic strength (μ) of 0.5 was maintained for each buffer by adding a calculated amount of potassium chloride. The reactions were initiated by adding 100 μl of a stock solution of the esters in water, ethanol or acetonitrile to 10 ml of preheated buffer solution in screw-capped test tubes, the final concentration of the compounds being $0.8-2 \times 10^{-4}$ M. The solutions were kept in a water-bath at constant temperature and at appropriate intervals, samples were withdrawn and chromatographed immediately. Pseudo-first-order rate constants for the degradation of the esters were determined from the slopes of linear plots of the logarithm of residual ester against time.

Hydrolysis kinetics in biological media. The hydrolysis of the esters was studied in human, rat, mouse, rabbit and guinea pig plasma, diluted to 80% with 0.05 M phosphate buffer (pH 7.40), as well as in whole human saliva at 37°C . The initial concentration of the compounds was 3×10^{-5} M in the plasma studies and $0.6-2 \times 10^{-4}$ M in the saliva studies. The reactions were initiated by adding 50 μl of a stock solution of the compounds in water, ethanol or acetonitrile to 5 ml of preheated plasma solution or saliva. The solutions were kept in a water-bath at 37°C , and at appropriate intervals, 250 μl samples were withdrawn and added to 500 μl of a 2% solution of zinc sulfate in methanol-water (1:1 v/v) or 1000 μl of ethanol in order to deproteinize the plasma and saliva. After mixing and centrifugation for 3 min at 13,000 rpm, 20 μl of the clear supernatant was analyzed by HPLC as described above.

Determination of lipophilicity parameters

The apparent partition coefficients (P) of ketobemidone and its esters were determined in the system octanol-0.05 M phosphate buffer (pH 7.40) at 22°C . These two phases were mutually saturated at 22°C before use. The compounds were dissolved in the aqueous buffer phase and the octanol-buffer mixtures were shaken for 1 h to reach a distribution equilibrium. The volumes of each phase were chosen so that the solute concentration in the aqueous phase, before and after distribution, could be readily measured using the HPLC method described above.

The partition coefficients were calculated from Eq. 1:

$$p = (C_i - C_w) / C_w \times (V_o / V_w) \quad (1)$$

where C_i and C_w represent the solute concentrations in the aqueous phase before and after distribution, respectively; V_w represents the volume of the aqueous and V_o the volume of the octanol phase.

The lipophilicity of the ester derivatives was also evaluated by means of reversed-phase HPLC. In this method the capacity factor (k') of a solute is taken as a measure of the relative lipophilicity:

$$k' = (t_r - t_o) / t_o \quad (2)$$

where t_r is the retention time of the solute and t_o is the retention time of the solvent.

Table 1. Physical and analytical data of various esters of ketobemidone^a.

Ester	R	Melting point ($^{\circ}\text{C}$)	Formula
II	$-\text{COCH}_3$	oil	$\text{C}_{17}\text{H}_{23}\text{NO}_3$
III	$-\text{COC}(\text{CH}_3)_3$	214-215	$\text{C}_{20}\text{H}_{30}\text{ClNO}_3$
IV	$-\text{COCH}_2\text{C}(\text{CH}_3)_3$	172-173	$\text{C}_{25}\text{H}_{35}\text{NO}_7$
V	$-\text{COC}_6\text{H}_5$	207-208	$\text{C}_{22}\text{H}_{26}\text{ClNO}_3$
VI	$-\text{COOCH}_3$	157-158	$\text{C}_{17}\text{H}_{24}\text{ClNO}_4$
VII	$-\text{COOC}_2\text{H}_5$	85- 86	$\text{C}_{18}\text{H}_{26}\text{ClNO}_4 \cdot \text{H}_2\text{O}$
VIII	$-\text{COOCH}(\text{CH}_3)_2$	171-172	$\text{C}_{19}\text{H}_{28}\text{ClNO}_4$
IX	$-\text{COOCH}_2\text{CH}(\text{CH}_3)_2$	159-160	$\text{C}_{20}\text{H}_{30}\text{ClNO}_4$
X	$-\text{COOC}_4\text{H}_9$	133-134	$\text{C}_{20}\text{H}_{30}\text{ClNO}_4$
XI	$-\text{COOC}_6\text{H}_{13}$	63- 64	$\text{C}_{22}\text{H}_{34}\text{ClNO}_4$

^a The ester II was isolated as the free base and ester IV as the fumarate salt. All other esters are hydrochloric acid salts.

Results and Discussion

The esters of ketobemidone (II-XI) prepared include alkyl esters (II-IV), an aryl ester (V) and several carbo-

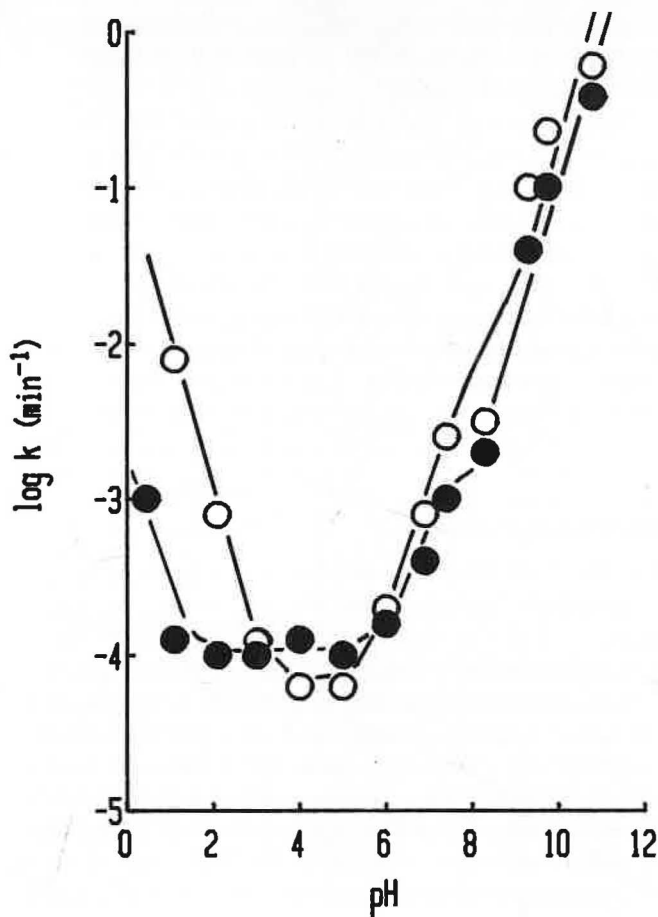


Fig. 1. The pH-rate profiles for the hydrolysis of the ketobemidone esters II (○) and VII (●) in aqueous solution ($\mu=0.5$) at 60°C.

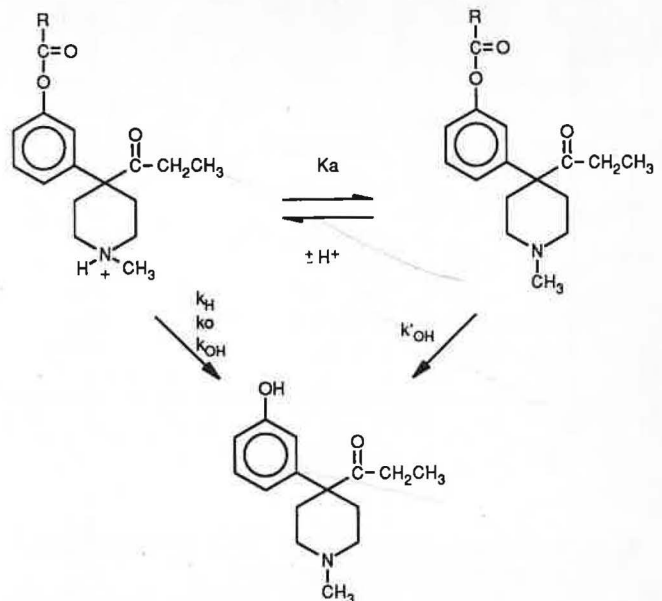
nate esters (VI-XI) containing both straight and branched alkyl chains. Such esters were expected to possess widely differing properties in terms of lipophilicity and chemical and enzymatic stability.

Chemical stability

All the esters underwent a quantitative degradation to ketobemidone in aqueous solution. The hydrolysis of the esters II, V and VII was examined over a wide pH-range whereas the other esters were studied only in neutral and basic solutions. The pH-rate profiles obtained for the esters II and VII are shown in Fig. 1, in which the observed pseudo-first-order rate constants (k_{obs}) have been plotted against pH.

The shape of the pH-rate profiles indicates that the hydrolysis of the esters is subject to specific acid- and base-catalyzed reactions as well as a water-catalyzed reaction. The profiles show a curvature at pH values around the $\text{p}K_a$ value of the compounds, indicating that the protonated form of the molecules undergoes hydroxide ion-catalyzed hydrolysis at a rate greater than that of the free base form. The rate equation accounting for the pH dependence of k_{obs} may be formulated as:

$$k_{\text{obs}} = k_H a_H = \frac{a_H}{a_H + K_a} + k_0 \frac{a_H}{a_H + K_a} + k_{\text{OH}} a_{\text{OH}} \frac{a_H}{a_H + K_a} + k'_{\text{OH}} a_{\text{OH}} \frac{K_a}{a_H + K_a} \quad (3)$$



Scheme 1

where a_H and a_{OH} refer to the hydrogen ion and hydroxide ion activities, respectively, $a_H / (a_H + K_a)$ and $K_a / (a_H + K_a)$ are the fractions of total ester in the protonated and free base forms, respectively, and K_a is the apparent ionization constant of the protonated amino group in the esters. The rate constant k_0 refers to the spontaneous or water-catalyzed hydrolysis of the protonated form of the ester, k_H is the specific acid-catalyzed rate constant for the protonated ester, and k_{OH} and k'_{OH} are the second-order rate constants for the hydroxide ion-catalyzed hydrolysis of the protonated and unprotonated ester species, respectively (Scheme 1). The a_{OH} values were calculated from the measured pH at 60°C according to the following equation [15]:

$$\log a_{\text{OH}} = \text{pH} - 13.02 \quad (4)$$

Values of the various rate and ionization constants derived from Eq. (3) are listed in Table 2. The $\text{p}K_a$ values derived kinetically were found to be in good agreement with those determined by titrimetry. Esterification of the phenol group in ketobemidone does not result in any significant change of the basicity of the amino function. Thus, whereas the $\text{p}K_a$ value for the amino group

Table 2. Rate data for the hydrolysis of various ketobemidone esters in aqueous solution ($\mu = 0.5$) at 60°C.

Compound	k_H ($\text{M}^{-1}\text{min}^{-1}$)	k_0 (min^{-1})	k_{OH} ($\text{M}^{-1}\text{min}^{-1}$)	k'_{OH} ($\text{M}^{-1}\text{min}^{-1}$)	$\text{p}K_a^a$
II	9.5×10^{-2}	6.0×10^{-5}	1520	265	7.8
III			145	45	7.7
IV			190	40	7.9
V	1.3×10^{-3}	4.4×10^{-5}	540	140	7.9
VI			1390	164	7.1
VII	2.3×10^{-3}	1.0×10^{-4}	1050	123	7.1
VIII			415	48	7.0
IX			1350	74	7.0
X			945	69	7.1
XI			1370	56	7.0

^a Kinetically determined values.

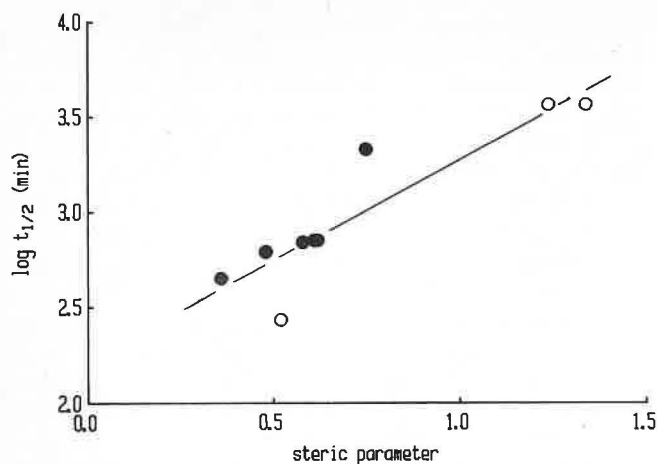


Fig. 2. Plot of $\log t_{1/2}$ (at pH 7.4 and 37°C) vs the steric parameter v for various ketobemidone esters.

The v values refer to the alkyl moiety in the acyl group and were taken from Charton [16]. (○) ketobemidone alkyl esters, (●) ketobemidone carbonate esters.

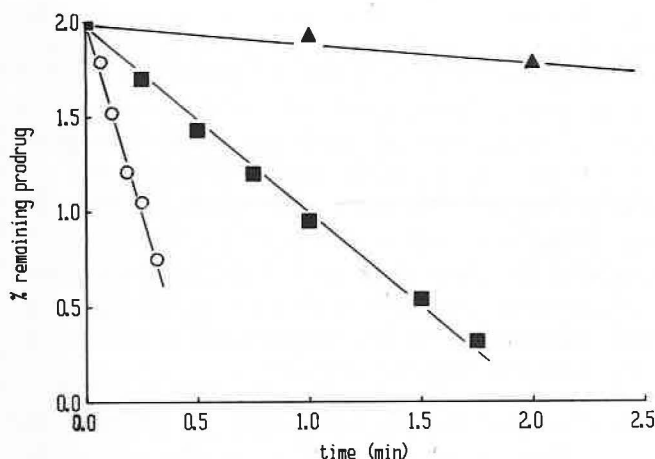


Fig. 3. First-order plots for the degradation of the ketobemidone esters III (■), IV (▲) and V (○) in 80% human plasma solutions (pH 7.40) at 37°C.

Table 3. Half-lives for the hydrolysis of various ketobemidone esters in buffer solutions (pH 7.4), 80% human plasma and human whole saliva.

Compound	Half-lives of hydrolysis (min)		
	pH 7.4 buffer ^a	80% human plasma ^b	whole saliva ^b
II	4.5 h (59 h) ^b	0.05	6.8
III	60 h	0.3	7.6
IV	60 h	1.8	295
V	11 h	0.08	4.0
VI	7.4 h (78 h) ^b	0.04	3.5
VII	10.3 h (162 h) ^b	0.03	5.1
VIII	35.6 h	0.04	4.9
IX	11.9 h	0.06	4.1
X	11.5 h	0.04	7.1
XI	11.8 h	0.11	4.4

^a At 60°C

^b At 37°C

in ketobemidone is 8.65 at 20°C [13], the amino group in the ester VII showed a pK_a value of 8.69 at 20°C as determined titrimetrically.

Comparing the reactivity of the esters II and VII in neutral and basic solutions shows that there is only a small difference between carboxylate and carbonate esters. The latter are, however, more stable than alkyl esters towards acid-catalyzed hydrolysis, cf. the k_H values for compounds II and VII. The stability in neutral and alkaline solutions is determined by the steric and polar effects exhibited by the alkyl, aryl or alkoxyalkyl groups. As seen from Fig. 2, a linear correlation exists between $\log t_{1/2}$ (pH 7.4) and the steric parameter v .

Hydrolysis in plasma

The susceptibility of the ketobemidone esters to undergo enzymatic hydrolysis was studied at 37°C in human plasma diluted to 80% with 0.01 M phosphate buffer solutions (pH 7.40). The rates of hydrolysis of all esters except compound VIII were found to follow first-order kinetics at an initial concentration of 3×10^{-5} M, as illustrated in Fig. 3 for some esters. In all cases the hydrolysis of the esters in the plasma solutions proceeded with the quantitative formation of ketobemidone. At an initial concentration of 3×10^{-5} M, the hydrolysis of ester VIII initially followed zero-order kinetics and, as the substrate depleted, it changed to follow first-order kinetics. This behaviour indicates that the enzymatic hydrolysis parameter K_m (i.e. the Michaelis constant) for this particular ester is less than 3×10^{-5} M [17]. The half-life of hydrolysis was calculated from the terminal linear part of the first-order plot. The observed half-lives in the plasma solutions are listed in Table 3, together with the half-lives of hydrolysis in pure buffer solutions at pH 7.40 but at 60°C. As it appears from the data, the rate of hydrolysis is markedly accelerated in plasma, the half-lives being only a few seconds except for the sterically most hindered ester IV which showed a half-life of 1.8 min.

To examine possible species variation in the plasma-catalyzed hydrolysis, the compounds IV and VIII were investigated in plasma from various other species. The half-lives of hydrolysis observed are listed in Table 4. As appears from the data, the carbonate ester VIII is hydrolyzed rapidly and at almost identical rates in the various plasma solutions. The 3,3-dimethylbutyryl ester (IV) is hydrolyzed more rapidly in mouse, guinea pig and rabbit plasma than in human plasma but, surprisingly, markedly slower in rat plasma.

Table 4. Half-lives of hydrolysis of two ketobemidone esters (IV and VIII) in 80% plasma solutions from various species (37°C).

Plasma	Half-lives (min)	
	IV	VIII
Human	1.8	0.04
Rat	14.6	0.04
Mouse	0.7	0.03
Guinea pig	0.6	0.08
Rabbit	0.2	0.03

Table 5. Partition coefficients (*P*) and chromatographic capacity factors (*k'*) of ketobemidone and ketobemidone esters.

Compound	log <i>P</i> ^a	log <i>k'</i>
Ketobemidone I	0.40	0.22
II	0.43	0.67
III	2.11	1.85
IV	2.55	2.18
V	2.41	1.99
VI	0.57	0.81
VII	1.11	1.17
VIII	1.54	1.51
IX	2.20	1.97
X	2.24	2.01
XI	3.20	2.77

^a Partition coefficient between octanol and aqueous buffer of pH 7.4 at 22°C.

Hydrolysis in saliva

The rate of degradation of the ketobemidone prodrug esters were determined in human whole saliva at 37°C in order to obtain information on possible saliva enzyme-catalyzed hydrolysis since human saliva is known to contain a variety of esterases [18-21]. Saliva (about 5 ml) was collected from one subject and was used immediately. Salivation was stimulated by paraffin chewing. The subject was fasted for 10 h prior to collection of saliva since preliminary experiments showed that the esterase activity of saliva was different before and after a meal. The esters were found to be fairly rapidly hydrolyzed when incubated in saliva at 37°C. The rate of hydrolysis proceeded in all cases according to first-order kinetics with half-life of 3-8 min, except for the ester IV which showed a half-life of 5 h (Table 3). In view of the rapid rate of saliva-catalyzed hydrolysis of the ketobemidone esters, the present findings make it important to consider such phenomenon in the development of buccal or sublingual hydrolysis-sensitive prodrugs or drug preparations.

Lipophilicity of ketobemidone esters

Partition coefficients (*P*) of ketobemidone and its esters as determined using an octanol-aqueous buffer system (pH 7.40) are listed in Table 5, along with reversed-phase HPLC capacity factors (*k'*) determined with the solvent system methanol-acetonitrile-0.1% phosphoric acid (5:15:80 v/v) containing 10⁻³ M triethylamine. The log *P* values given actually represent the distribution coefficients since the compounds at pH 7.4 are only partly present in their unprotonated forms. The results obtain show that the esters are all more lipophilic than the parent ketobemidone. The difference in the log *P* values for the derivatives is as expected on the basis of the π substituent parameters. Thus, the increase in log *P* from the methyl carbonate ester (VI) to the ethyl carbonate ester (VII) amounts to 0.54, which agrees with the π value of 0.52 for a methylene group [22].

As has been observed for various compounds (e.g. [23]), a linear relationship exists between log *P* and log *k'* (Fig. 4). As can be seen from Fig. 4, ketobemidone

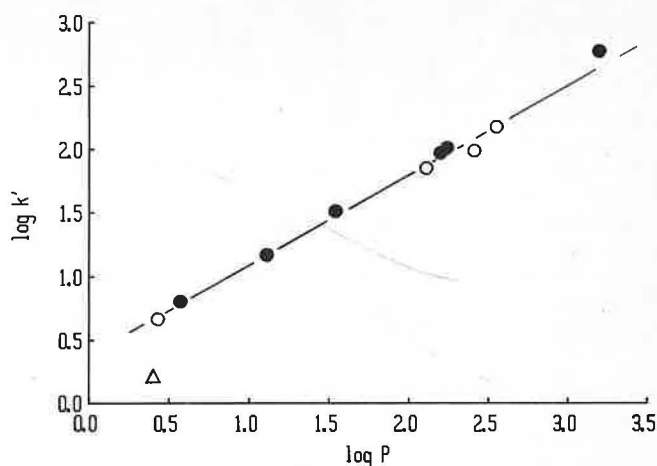


Fig. 4. Plot of log *P* (at pH 7.4) versus log *k'* for ketobemidone (Δ) ketobemidone alkyl and aryl esters (○) and ketobemidone carbonate esters (●).

The regression equation is: log *k'* = - 0.72 log *P* + 0.37 (*r* = 0.996; *n*=10).

shows a marked deviation from the plot encompassing the esters. This may probably be ascribed to the ability of the free phenolic group in ketobemidone to form a hydrogen bond with octanol, thereby increasing the log *P* value.

Conclusions

The results obtained suggest that derivatization of the phenolic group in ketobemidone to form carboxylic acid or carbonate esters may be a useful prodrug approach. The esters are much more lipophilic than the parent drug and hence potentially more capable of penetrating the buccal mucosal barrier. Due to the presence of the tertiary amino group, the esters are readily soluble in water in the form of hydrochloric acid salts. Compared with the other esters, the 3,3-dimethylbutyryl ester IV shows a relatively high resistance to being enzymatically hydrolyzed by saliva. This property, along with its facile plasma-catalyzed hydrolysis and high lipophilicity, makes this ester the most promising prodrug for buccal delivery.

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