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Short Communications

An alternative prodrug approach for reducing presystemic metabolism of drugs

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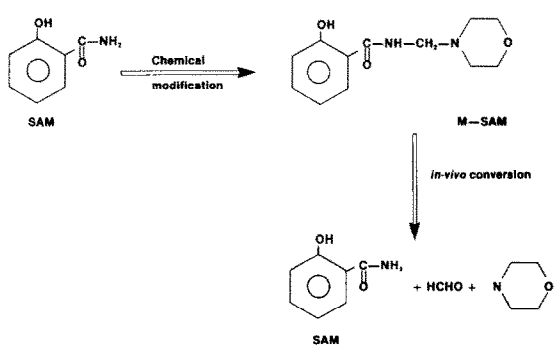
Several drugs are known to undergo extensive presystemic metabolism. As a consequence oral delivery of such drugs is a major pharmaceutical problem. A prodrug approach has been cited as a potential solution to this problem. However, the stability of a prodrug is a critical factor in the successful delivery of a drug (Notari, 1977). If a prodrug is sufficiently stable to withstand presystemic metabolism, it may then resist bioconversion to yield the active drug in vivo. Conversely if it is rapidly converted to the active drug, it may not protect against presystemic metabolism. In the past, several attempts have been made to improve the bioavailability of drugs by esterification of the phenolic groups at which presystemic metabolism takes place. However, little or no improvement in bioavailability was observed in animals, on account of the high esterase activity in the gut wall (Niphadkar, 1982). The overall objective of our study was to determine whether presystemic metabolism of drugs can be prevented or reduced by structural modification through prodrug formation without derivatizing the group at which presystemic metabolism takes place. In the present report our results on the bioavailability of salicylamide following oral administration of a prodrug are discussed.

Salicylamide (SAM), an analgesic and antipyretic (Way et al., 1953) which is known to undergo extensive presystemic conjugation metabolism in both man (> 90%, Riegelman et al., 1973) and rabbits (95%, Shibasaki et al., 1981), was chosen as a model drug for this study. The amide functional group, neighboring to the phenolic group that is involved in the presystemic metabolism, was transformed into an N-Mannich base, namely N-morpholinomethyl salicylamide (M-SAM) (Scheme 1) by conventional synthetic



Scheme 1

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method (Watase et al., 1971). The conversion of this prodrug to SAM is chemically mediated and hence is independent of availability of any enzymes. The generation of SAM which is a pH dependent process occurs far more rapidly at pH 7.4 ($T_{1/2}$, 35 min at 38°C) than at pH 2.0–4.0 ($T_{1/2}$, 148–190 min at 38°C). The rate determining step in the conversion of N-Mannich base to an amide involves (Bundgaard and Johansen, 1980) unimolecular N–C bond cleavage with the formation of amide anion and immonium cation which are subsequently converted to amide, formaldehyde and amine.

A group of 5 rabbits received orally SAM (100 mg/kg) or M-SAM (equivalent to 100 mg/kg of SAM) in a random crossover design, after an overnight fast, in a 15 ml solution of propylene glycol/ethanol/0.01N hydrochloric acid (10:10:80). The propylene glycol and ethanol were used to solubilize SAM and M-SAM, whereas hydrochloric acid was used to solubilize M-SAM and slow down its in vitro conversion to SAM. Multiple blood samples were obtained through the marginal ear vein of the rabbit over a period of 360 min after the administration. Plasma was immediately separated by centrifugation. A set of plasma samples was immediately quenched with 20% phosphoric acid and frozen until analyzed, to prevent in vitro conversion of M-SAM to SAM. The other set was kept at room temperature for at least 4 h to let the conversion proceed to completion. SAM concentration in all the samples was determined by a high-pressure liquid chromatographic method using fluorescent detection (Gautam et al., 1981). The area under the SAM plasma concentration versus time curve from time zero to infinity (AUC_0^∞) was calculated by the trapezoidal rule.

A representative plot of SAM plasma concentration versus time following oral administration of SAM and M-SAM to one rabbit on two separate occasions is shown in Fig. 1. In general, SAM plasma levels were significantly higher following the prodrug administration than after salicylamide administration. The percent increase in AUC_0^∞ ranged from 88–520% with a mean ± S.D. of 226 ± 180.7 (Table 1). The SAM concentration after M-SAM administration was higher in the

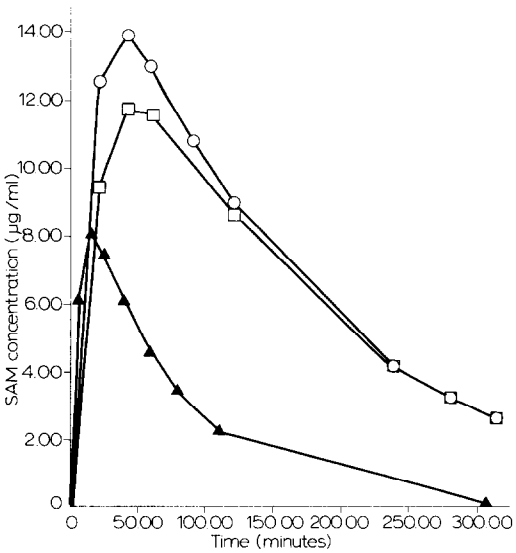

Fig. 1. Plasma concentration of salicylamide following oral administration of SAM (100 mg/kg) and its prodrug M-SAM (equivalent to 100 mg/kg SAM) to the rabbit. ▲, SAM plasma levels following administration of SAM; □, quenched SAM plasma levels following administration of M-SAM; ○, unquenched SAM plasma levels following administration of M-SAM.

TABLE 1

AREA UNDER THE PLASMA SAM CONCENTRATION VERSUS TIME CURVE $(AUC)_0^\infty$ FOLLOWING ORAL ADMINISTRATION OF A SINGLE 100 mg/kg DOSE OF SAM OR ITS EQUIVALENT OF M-SAM TO RABBITS

Rabbit no.	AUC_0 (µg·min/ml)		% Increase in AUC_0^∞ [a]
	SAM following SAM	SAM following M-SAM	
1	747	2828	279
2	316	1958	520
3	1814	3880	114
4	1460	3309	127
5	1381	2591	88
Mean ± SD	1144 ± 538	2913 ± 650 [b]	226 ± 180.7

[a] % Increase in AUC_0^∞ of SAM after M-SAM administration over the corresponding administration of SAM.

[b] Significantly different at $P < 0.05$ from SAM administration.

unquenched samples as compared to the quenched initial samples.

The higher SAM concentration observed in the unquenched samples indicates that the intact M-SAM was present in the general circulation. This could only be possible if at least a part of the prodrug dose was absorbed through the gastrointestinal tract as the intact prodrug without getting converted to the drug or undergoing first pass conjugation metabolism. Preliminary intravenous studies indicate that M-SAM is converted quantitatively to SAM in rabbits. The mean $AUC_0^\infty \pm$ S.D. of SAM after intravenous administration of SAM (50 mg/kg) and M-SAM (equivalent to 50 mg/kg of SAM) on different occasions to three rabbits was 2452 ± 105 and 2429 ± 300 $\mu g \cdot$ min/ml, respectively. Since SAM is known to be absorbed completely after oral administration in rabbits (Shibasaki et al., 1981), the observed increase in availability of SAM after M-SAM administration can be attributed to the reduction in the extent of presystemic metabolism. In conclusion, these preliminary results strongly suggest that structural modification of drugs through prodrug formation without derivatizing the group(s) at which presystemic metabolism takes place, may provide an alternative prodrug approach for improving delivery of drugs that are subjected to extensive presystemic metabolism.

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References

Bundgaard, H. and Johansen, M., Prodrugs as drug delivery systems IV: N-Mannich bases as potential novel prodrugs for amides, ureides, amines and other NH-acidic compounds, J. Pharm. Sci., 69 (1980) 44–46.

Gautam, S.R., Chungi, V., Hussain, A., Babhair, S., and Papadimitrai, D., A direct and sensitive method for the determination of salicylamide in microplasma samples by high-performance liquid chromatography using fluorescence detection. Anal. Lett. 14 (1981) 577–582.

Niphadkar, P.V., Some In-Vitro and In-Vivo Studies on Prodrugs of Acetaminophen (APAP), Thesis, The University of Kansas, Lawrence, 1982, pp. 82–83.

Notari, R.E., Design of Biopharmaceutical Properties through Prodrugs and Analogs, American Pharmaceutical Association, Washington, DC, 1977, p. 76.

Riegelman, S. and Rowland, M., Effect of route of administration on drug disposition. J. Pharmacokinetics Biopharm., 1 (1973) 419–434.

Shibasaki, J., Konishi, R., Koike, M., Imamura, A. and Sueyasu, M., Some quantitative evaluation of first-pass metabolism of salicylamide in rabbit and rat. J. Pharm. Dyn., 4 (1981) 91.

Watase, Y., Terao, Y. and Sekiya, M., Synthesis of N-(Alkylaminomethyl) amides. Chem. Pharm. Bull., 21 (1973) 2775–2778.

Way, E.L., Takemori, A.E., Smith, G.E., Anderson, H.H. and Brodie, D.C., The toxicity and analgesic activity of some congeners of salicylamide. J. Pharmacol. Exp. Ther., 108 (1953) 450.