radioactive isoniazid in tuberculosis patients. *J. Am. med. Ass.*, **151**, 1384–1388.

BLASCHKE, T.F. & MELMON, K.L. (1980). Hydralazine, Chaper 32, Antihypertensive Agents and The Drug Therapy of Hypertension. In *The Pharmacological Basis of Therapeutics*, Sixth Ed., eds Gilman, A.G., Goodman, L.S. & Gilman, A. 799–801. New York: Macmillan.

DES PREZ, R. & BOONE, I.V. (1961). Metabolism of ^{14}C-isoniazid in humans. *Am. Rev. resp. Dis.*, **84**, 42–51.

ELLARD, G.A. & GAMMON, P.T. (1976). Pharmacokinetics of isoniazid metabolism in man. *J. Pharmacokinet. Biopharm.*, **4**, 83–113.

ELLARD, G.A., GAMMON, P.T. & TIITINEN, H. (1973). Determination of the acetylator phenotype from the ratio of the urinary excretion of acetylisoniazid to acid-labile isoniazid: A study in Finnish Lapland. *Tubercle*, **54**, 201–210.

EVANS, D.A.P., MANLEY, K.A. & McKUSICK, V.A. (1960). Genetic control of isoniazid metabolism in man. *Br. med. J.*, **2**, 485–491.

HARLAND, S.J., FACCHINI, V. & TIMBRELL, J.A. (1980). Hydralazine-induced lupus erythematosus-like syndrome in a patient of the rapid acetylator phenotype. *Br. med. J.*, **281**, 273–274.

JENNE, J.W., MacDONALD, F.M. & MENDOZA, E. (1961). A study of the renal clearance, metabolic inactivation rates, and serum fall-off interaction of isoniazid and para-aminosalicylic acid in man. *Am. Rev. resp. Dis.*, **84**, 371–378.

KARCH, F.E. & LASAGNA, L. (1975). Adverse drug reactions. *J. Am. med. Ass.*, **234**, 1236–1241.

KIRKENDALL, W.M. & PAGE, E.B. (1958). Polyneuritis occuring during hydralazine therapy. *J. Am. med. Ass.*, **167**, 427–432.

KOCH-WESER, J. (1976). Hydralazine. *New Engl. J. Med.*, **295**, 320–323.

LARSSON, R., KARLSSON, E. & MOLIN, L. (1977). Spontaneous systemic lupus erythematosus and acetylator phenotype. *Acta med. Scand.*, **201**, 223–226.

LUNDE, P.K.M., FRISLID, K. & HANSTEEN, V. (1977). Disease and acetylation polymorphism. *Clin. Pharmacokin.*, **2**, 182–197.

OLSON, W.A., DAYTON, P.G., ISRAILI, Z.H. & PRUITT, A.W. (1977). Spectrophotofluorometric assay for isoniazid and acetyl isoniazid in plasma adapted to pediatric studies. *Clin. Chem.*, **23**, 747–748.

PERRY, H.M., Jr. (1973). Late toxicity to hydralazine resembling systemic lupus erythematosus or rheumatoid arthritis. *Am. J. Med.*, **54**, 58–72.

PERRY, H.M., Jr., TAN, E.M., CARMODY, S. & SAKAMOTO, A. (1970). Relationship of acetyl transferase activity to antinuclear antibodies and toxic symptoms in hypertensive patients treated with hydralazine. *J. lab. clin. Med.*, **76**, 114–125.

RASKIN, N.H. & FISHMAN, R.A. (1965). Pyridoxine-deficiency neuropathy due to hydralazine. *New Engl. J. Med.*, **273**, 1182–1185.

SUNAHARA, S., URANO, M. & OGAWA, M. (1961). Genetical and geographical studies on isoniazid inactivation. *Science*, **134**, 1530–1531.

TALSETH, T. (1977). Clinical pharmacokinetics of hydralazine. *Clin. Pharmacokin.*, **2**, 317–329.

TIITINEN, H., MATTILA, M.J. & ERIKSSON, A.W. (1973). Isoniazid inactivation in Finns and Lapps as demonstrated by various methods. *Am. Rev. resp. Dis.*, **108**, 375–378.

WEBER, W.W. & HEIN, D.W. (1979). Clinical pharmacokinetics of isoniazid. *Clin. Pharmacokin.*, **4**, 401–422.

HIGH UNBOUND FRACTION OF SALICYLATE IN PLASMA DURING INTOXICATION

A 14 year old girl with a cumbersome psychosocial background was admitted and stated the intake of 80 analgesic tablets equal to 40 g of acetylsalicylic acid and 0.8 g of codeine. She had gastric lavage immediately and charcoal suspension was administered. After 12 h her general condition deteriorated and she was referred to the intensive care unit in a state of superficial coma and moderate hyperventilation. Supportive therapy including alkalinisation and i.v. fluid was maintained and 5 h later she woke up.

Determination of total and unbound plasma concentrations were performed in samples taken at admission and up to 38 h thereafter (Brodie, Udenfriend & Coburn, 1944; Ehrnebo, Agurell, Jalling & Boréus, 1971; Behm & Wagner, 1979). The percentage of unbound salicylate decreased from 60 to 17 as the total concentration fell from 925 to 83 μg/ml (Figure 1). Albumin concentration in plasma ranged between 38–45 g/l. In a second intoxicated patient the salicylate concentration decreased from 745 to 69

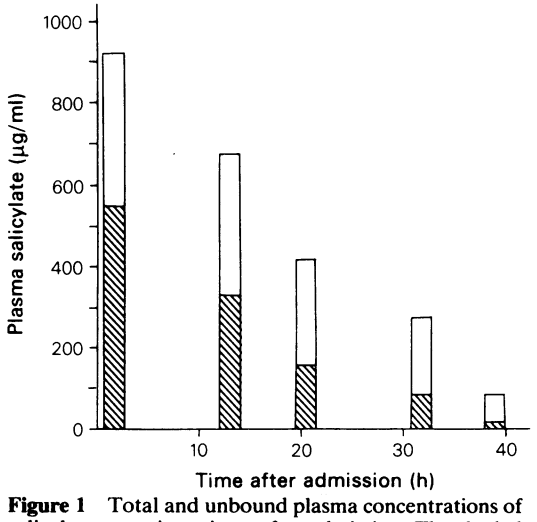

Figure 1 Total and unbound plasma concentrations of salicylate at various times after admission. The shaded area indicates the free concentration.

μg/ml while the unbound concentration decreased from 74% to 20%.

It is now well recognised that the unbound fraction of salicylate increases with the plasma concentration already within the therapeutic range as the binding capacity of the albumin is partly saturated (Borga, Odar-Cederlöf, Ringberger & Norlin, 1976; Wosilait, 1976). The classical studies which have revealed the saturable metabolism of salicylate have dealt with urinary excretion of its metabolites (Levy, 1965; Levy, Tsuchiya & Amsel, 1972). In plasma one has to determine the unbound salicylate concentration to appreciate the obvious capacity limited elimination of this drug (Aarons, Bochner & Rowland, 1977; Ekstrand, Alván & Borga, 1979; Furst, Tozer & Melmon, 1979). The higher proportion of unbound drug at high concentration implies that even more pharmacological and toxic effects should be expected than inferred from the total concentration. The therapeutic range has been stated to be 200–350 μg/ml (Hart, 1980). Capacity limited elimination markedly enhances the potential for variability in unbound and thus pharmacologically active drug between patients and it implies that small changes in the dose might correspond to great changes in unbound concentration of salicylate in plasma. In a recent study the unbound salicylate concentrations were found to increase up to 24-fold when the daily dose was increased from 2.0 to 4.5 g (Ekstrand, Alván, Magnusson, Oliw, Palmer & Rane, 1981).

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References

AARONS, L.J., BOCHNER, F. & ROWLAND, M. (1977). A chronic dose ranging kinetic study of salicylate in man. *Br. J. Pharmac.*, **61**, 456P–457P.

BEHM, H.L. & WAGNER, J.G. (1979). Errors in interpretation of data from equilibrium dialysis protein binding experiments. *Res. Comm. Chem. Path. Pharmac.*, **26**, 145–160.

BORGA, O., ODAR-CEDERLÖF, I., RINGBERGER, V.A. & NORLIN, A. (1976). Protein binding of salicylate in uremic and normal plasma. *Clin. Pharmac. Ther.*, **20**, 464–475.

BRODIE, B.B., UDENFRIEND, S. & COBURN, A.F. (1944). The determination of salicylic acid in plasma. *J. Pharmac. exp. Ther.*, **80**, 114–117.

EHRNEBO, M., AGURELL, S., JALLING, B. & BORÉUS, L.O. (1971). Age differences in drug binding by plasma proteins: studies on human foetuses, neonates and adults. *Eur. J. clin. Pharmac.*, **3**, 189–193.

EKSTRAND, R., ALVÁN, G. & BORGA, O. (1979). Concentration dependent plasma protein binding of salicylate in rheumatoid patients. *Clin. Pharmacokin.*, **4**, 137–143.

EKSTRAND, R., ALVÁN, G., MAGNUSSON, A., OLIW, E., PALMÉR, L. & RANE, A. (1981). Clinical effect of indomethacin suppositories during salicylate therapy. *Scand. J. Rheumatol.* (in press).

FURST, D.E., TOZER, T.N. & MELMON, K.L. (1979). Salicylate clearance, the resultant of protein binding and metabolism. *Clin. Pharmac. Ther.*, **26**, 308–390.

HART, F.D. (1980). Rheumatic disorders. In *Drug Treatment*, ed Avery, G.S. Sydney and New York: ADIS Press.

LEVY, G. (1965). Pharmacokinetics of salicylate elimination in man. *J. pharm. Sci.*, **54**, 959–967.

LEVY, G., TSUCHIYA, T. & AMSEL, L.P. (1972). Limited capacity for salicyl phenolic glucuronide formation and its effect in the kinetics of salicylate elimination in man. *Clin. Pharmac. Ther.*, **13**, 258–268.

WOSILAIT, W.D. (1976). Theoretical analysis of the binding of salicylate by human serum albumin: the relationship between free and bound drug and therapeutic levels. *Eur. J. clin. Pharmac.*, **9**, 285–290.

PROTECTION AGAINST ASPIRIN-INDUCED BLOOD LOSS IN MAN: ASSESSMENT OF A NEW MUCOLYTIC AGENT

Therapeutic agents which are of value in peptic ulcer may be classified as those which reduce acid secretion and those which protect gastric mucosa against injury. A major difficulty in the development of new agents is to establish their value in man after exhaustive evaluation in animal models. Although their value will eventually depend on results from controlled trials, it would be useful to have some indication of their therapeutic effect in man before proceeding to the clinical trial situation. We have tried to do this with a new mucolytic agent by measuring the reduction in blood loss caused by aspirin in ten healthy volunteers.

A standard method for estimating gastric mucosal damage by non steroidal anti-inflammatory drugs depends on measurement of faecal blood loss using