Influence of phenylbutazone on bile flow in the rat

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Summary. Phenylbutazone, a well-known enzyme inducer, at a dose of 80 mg · kg^{-1} once daily for 8 days increases liver weight and bile flow expressed per g of liver ($p < 0.01$). The bile salt secretory rate is not increased.

Drugs known to be hepatic microsomal enzyme inducers increase liver weight, cause a hypertrophy of the smooth endoplasmic reticulum in the hepatocytes and increase the activity of several microsomal enzymes, especially cytochrome P 450[1-3]. Some of those inducers, such as phenobarbital, increase bile flow mainly of the bile salt non-dependent fraction[4], others such as 3 methylchlorantrene and 3-4 benzpyrene do not[5]. It has been reported that phenylbutazone, a well-known enzyme inducer[1], does not significantly increase bile flow[5,6]. The result is questionable, because there is no evidence of induction in the data presented: no increase in liver weight, no decrease in zoxazolamine paralysis time. We were able to obtain a significant increase in liver weight after phenylbutazone administration. The purpose of this work was to study bile flow in phenylbutazone-treated rats.

Bile flow and bile salt secretory rate in control and phenylbutazone induced rats

N	Control 10		Phenylbutazone 7
B.wt/l.wt[a] × 100	3.07[e] ± 0.10	$p < 0.05$	3.25 ± 0.08
BF[b] (µl · min^{-1} · 100 g^{-1} b.wt)	7.52 ± 0.86	$p < 0.01$	9.44 ± 1.15
BF (µl · min^{-1} · g^{-1} l.wt)	2.44 ± 0.21	$p < 0.01$	2.89 ± 0.27
BS[c] (µmole · ml^{-1})	44.06 ± 7.02	$p < 0.01$	34.60 ± 6.26
BSSR[d] (µmole · min^{-1} · 100 g^{-1} b.wt)	0.331 ± 0.065	NS	0.324 ± 0.055
BSSR (µmole · min^{-1} · g^{-1} l.wt)	0.107 ± 0.020	NS	0.099 ± 0.016

[a] B.wt/l.wt = body weight/liver weight; [b] BF = bile flow; [c] BS = bile salt concentration; [d] BSSR = bile salt secretory rate; [e] mean ± SD.

Materials and methods. Male Wistar rats (Evic Ceba, Blanquefort) weighing 170-220 g were used. Sodium phenylbutazone (kindly supplied by Geigy Pharmaceuticals) dissolved in corn oil was given orally at a dose of 80 mg · kg^{-1} once daily at 16.00 h for 8 days. The experiments were performed the morning following the last dose; 16 h before the experiment, rats were not allowed to eat, water was given ad libitum. The animals were anesthetized i.p. with pentobarbital sodium. Rectal temperature was maintained throughout the experiment, between 37.5 and 38.5 °C on a heating table. The common bile duct was cannulated. Bile was then collected during the first 30 min in 3 10-min samples and weighed to measure bile flow. At the end of each experiment, the portal vein was clamped, the hepatic veins were cut and the liver was immediately removed and washed in a beaker containing cold 0.15 moles NaCl. The liver was blotted dry and weighed. In the control group, rats received the volume of corn oil.

Bile acids concentration in bile was measured by an enzymatic method[7] using 3 α-hydroxysteroid dehydrogenase (Worthington, Freehold, New-Jersey, USA). Details of the technique are described elsewhere[4]. Statistical analysis of the results was performed using the student's t-test.

Results and discussion. The influence of phenylbutazone on liver weight, bile flow, bile salt concentration and bile salt secretory rate is shown in the table. Phenylbutazone significantly increases liver weight and bile flow whether expressed per 100 g b.wt or per g l wt. Bile salt secretory rate remains unchanged. Phenylbutazone is a potent enzyme inducer[1]. The significant increase in liver weight is the proof that our rats were effectively induced. The failure reported by others[5] to induce rats may have several explanations: Strain and interindividual variations in inducibility of hepatic microsomal drug metabolizing enzymes have been reported in the rat[8]. The age of the animals as well as time of administration during the day may be of importance[9].

Eventhough there was no true induction, bile flow was increased (19%) but not significantly[5]; this may be due to the small number of rats. Phenobarbital[4] is a more potent choleretic than phenylbutazone (50% increase in bile flow versus 25%). However when expressed per g of liver, this is not true anymore.

It is reasonable to assume, even though we have not measured erythritol clearance, that phenylbutazone, like phenobarbital, increases the bile salt non dependent fraction. Whether there is a direct relationship between phenylbutazone enzyme induction and increment in bile flow is not known. It has been pointed out that the increase in bile flow observed after barbiturate treatment in the rat is possibly independent of the hepatic microsomal enzyme induction produced by these drugs[10].

It is conceivable that phenylbutazone increases bile flow through an osmotic choleresis. 48 h after 14C phenylbutazone administration 34.7% of the total radioactivity is recovered in the stool, against 60.8% in the urine[11]. Phenylbutazone can be excreted freely into bile, the main metabolite oxyphenbutazone, obtained by side chain hydroxylation, is excreted in larger amount[11].

The injection of phenylbutazone for several days results in a sharp increase in the drug's own metabolism[12]. At the time of the experiment (18 h after the last injection) it might be possible that most of the phenylbutazone and its metabolites have been eliminated and therefore may not account for the osmotic choleresis.

1 A.H. Conney, Pharmac. Rev. *19*, 317 (1967).
2 H. Remmer, J. clin. Pharmac. *5*, 116 (1972).
3 W. Staubly, R. Hess and E.R. Weibel, J. Cell Biol. *42*, 92 (1969).
4 P. Berthelot, S. Erlinger, D. Dhumeaux and A.M. Preaux, Am. J. Physiol. *210*, 809 (1970).
5 C.D. Klaassen, J. Pharmac. expt. Ther. *168*, 218 (1969).
6 C.D. Klaassen, Biochem. Pharm. *19*, 1241 (1970).
7 R. Iwata and K. Yamasaki, J. Biochem., Tokio *56*, 424 (1964).
8 A. Jori and R. Pescador, Chem. biol. Interac. *8*, 297 (1974).
9 E.S. Vessel, Ann. N.Y. Acad. Sci. *151*, 900 (1968).
10 J.P. Capron, M. Dumont, G. Feeldman and S. Erlinger, Digestion *15*, 556 (1977).
11 O.M. Bakke, G.H. Draffan and D.S. Davies, Xenobiotica *4*, 237 (1974).
12 R.M. Welch, Y.E. Harrison, A.H. Conney and J.J. Burns, Clin. Pharmac. Ther. *10*, 817 (1967).