Effect of aspirin on the fate of bishydroxycoumarin in the rat

Coldwell & Zawidzka (1968) showed that the oral administration of a single dose of aspirin (100 mg/kg) to male rats on a regimen of the anticoagulant drug, bishydroxycoumarin, decreased the one-stage prothrombin time of blood collected 20 h after administration of the analgesic. Subsequently, this action of aspirin was observed in female and male rats after chronic dosing and was produced even more intensely by an equivalent amount of sodium salicylate, while several other analgesics were without any effect (Zawidzka & Coldwell, 1970). Analysis of the serum samples obtained from some of these animals for bishydroxycoumarin, using the spectrophotometric method of Nagashmia, Levy & Nelson (1968), suggested that aspirin might be affecting the serum bishydroxycoumarin concentration. This lead to the possible mechanism of the observed anti-bishydroxycoumarin effect of aspirin and sodium salicylate has now been investigated further.

Male albino rats of the Wistar strain, 175–200 g, acclimatized to the laboratory environment for at least one week, were dosed intraperitoneally with bishydroxycoumarin daily for 3 days at 2·0, 1·5 and 1·5 mg/100 g, respectively. The dose administered on day 3 included 171·4 μg/100 g of [^{14}C]bishydroxycoumarin having a specific activity of 2·58 mCi/mmol. Simultaneously with the administration of bishydroxycoumarin on day 3, aspirin (100 mg/kg)was administered orally to 6 of the 11 animals. The animals were then placed immediately in metabolism cages with free access to water; food was made available for a short period 24 h after the final drug administration. Tail blood specimens (10 μl) were taken at 0·5, 1, 2, 4, 7, 12, and 24 h and urine and faeces were each collected over the periods from 0 to 24 h and 24 to 48 h after the final drug administration. The samples were analysed for radioactivity using an accepted liquid scintillation counting procedure (radioactivity is expressed as unmetabolized bishydroxycoumarin).

The blood decay profiles for bishydroxycoumarin in the presence and absence

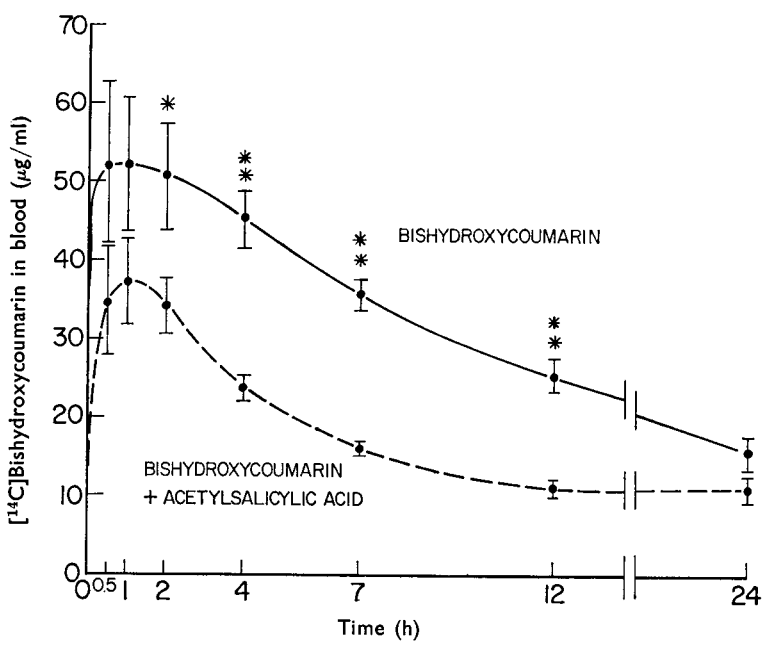

FIG. 1. Blood decay profiles for [^{14}C]bishydroxycoumarin administered alone and with aspirin. $*P < 0{\cdot}01$. $**P < 0{\cdot}001$.

of aspirin are illustrated in Fig. 1. The concentrations in the animals given bishydroxycoumarin alone were significantly higher than those in the animals that received aspirin with the anticoagulant in the period from 2 to 12 h after the final drug administration, the differences being highly significant ($P < 0{\cdot}001$) at the 4, 7, and 12 h intervals. After 24 h the blood bishydroxycoumarin concentrations were similar in each group. The high standard errors for the mean levels at 0·5 and 1 h indicate the variability in the rate of absorption of this drug when given intraperitoneally.

The half-life of bishydroxycoumarin in the blood, during the period of relatively rapid disappearance, in the presence and absence of aspirin, was 4·5 and 9·9 h, respectively. During these periods, which were 1 to 10 h in the former group and 1 to 12 h in the latter, the rate of disappearance of bishydroxycoumarin from the blood followed apparent first-order kinetics. Nagashima, Levy & Back (1968) reported plasma $T_{\frac{1}{2}}$ values for bishydroxycoumarin from 4·6 to 5·6 h in male, Sprague-Dawley rats of 430–470 g after single intravenous doses of the drug ranging from 2 to 20 mg/kg.

Christensen (1964) obtained a value of 9·2 h in white female rats of about 190 g that were injected intravenously with 5·2 mg of the anticoagulant. Differences in $T_{\frac{1}{2}}$ values of bishydroxycoumarin no doubt reflect differences in the species, strain and weight of animals used and also the dose and route of administration.

The amounts of bishydroxycoumarin recovered in the urine and faeces from the two groups of animals during the 48 h after the final administration of the drugs were not significantly different at either the 24 h or 48 h collection periods. Approximately 66% of the dose of bishydroxycoumarin administered on day 3 was recovered during the subsequent 48 h. Elimination of a significant amount of bishydroxycoumarin in the faeces (43–45%) was confirmed (Christensen, 1965).

We are not aware of any previous reports indicating that the administration of a therapeutic dose of aspirin decreases the circulating blood levels of bishydroxycoumarin during a time when there were significant salicylate levels in the blood. It has been suggested that salicylates may compete with coumarin anticoagulants for protein binding sites (Formiller & Cohon, 1969) which could result in more rapid excretion of the unbound drug. Such transient effects might be obscured in the analysis of the 24 h urine and faeces collections. The slight change in physiologic pH resulting from the concomitant administration of aspirin might be a factor affecting the distribution of bishydroxycoumarin since its binding to albumin is known to vary markedly with changes in the acidity of the environment (Nagashima & others, 1968).

Our thanks are due to Messrs. G. Solomonraj and W. Zeitz for technical assistance.

Research Laboratories,
Food and Drug Directorate,
Department of National Health and Welfare,
Ottawa, Canada.

BLAKE B. COLDWELL
BARRY H. THOMAS

November 9, 1970

REFERENCES

CHRISTENSEN, F. (1964). *Acta pharmac. tox.*, **21**, 307–312.
CHRISTENSEN, F. (1965). *Ibid.*, **22**, 141–151.
COLDWELL, B. B. & ZAWIDZKA, Z. (1968). *Blood*, **32**, 945–949.
FORMILLER, M. & COHON, M. S. (1969). *Am. J. Hosp. Pharm.*, **26**, 574–582.
NAGASHIMA, R., LEVY, G. & BACK, N. (1968). *J. pharm. Sci.*, **57**, 68–71.
NAGASHIMA, R., LEVY, G. & NELSON, E. (1968). *Ibid.*, **57**, 58–67.
ZAWIDZKA, Z. & COLDWELL, B. B. (1970). *Proc. Can. Fed. biol. Soc.*, **13**, Abst. No. 414.