SPECIAL ARTICLES

p-AMINOBENZOIC ACID DETOXICATION OF CARBARSONE (p-CARBAMINO PHENYL ARSONIC ACID) AND CERTAIN OTHER PENTAVALENT PHENYL ARSONATES ADMINISTERED IN MASSIVE DOSES TO RATS[1]

UNPUBLISHED studies pursued in our laboratory during the past two years have revealed that carbarsone, a drug widely used in the treatment of amebiasis, possesses trypanocidal properties, especially against *Trypanosoma equiperdum*.

In view of (a) the remarkable inhibition of the bactericidal[2,3] and malariacidal[4,5] action of certain sulfonamide drugs by the chemically similarly constituted *p*-aminobenzoic acid and (b) the fact that carbarsone possesses a *p*-amino phenyl group, it was of interest to determine what inhibitory effect, if any, *p*-aminobenzoic acid might exert on the trypanocidal action of carbarsone.

In order to avoid masking any minimal effects, both high and low doses of carbarsone that previous experience had shown to be effective in clearing the blood stream of trypanosomes were given, with and without the addition of *p*-aminobenzoic acid, to a series of infected rats. Two groups of control rats were set up: (1) infected rats receiving *p*-aminobenzoic acid alone and (2) uninfected rats receiving a high dose of carbarsone alone. In this preliminary experiment no inhibition of trypanosome multiplication was detected in the rats that received *p*-aminobenzoic acid alone. In those rats that received the smaller doses of carbarsone plus *p*-aminobenzoic acid, the trypanosomes, after disappearing from the blood stream, eventually reappeared, the animals finally dying of the disease. It was particularly interesting to note that the majority of rats that had received the high doses of carbarsone plus *p*-aminobenzoic acid survived; on the other hand, a large proportion of the controls, *i.e.*, rats which received the same high dose of carbarsone without the addition of *p*-aminobenzoic acid, died.

From this experiment two tentative deductions were drawn: (1) that *p*-aminobenzoic acid does not inhibit the trypanocidal action of carbarsone, and (2)

TABLE 1

PROTECTION OF RATS AGAINST CERTAIN ORGANIC ARSENICALS BY *p*-AMINOBENZOIC ACID

Drug dose and mode of administration	Dose of *p*-aminobenzoic acid and frequency of administration	Number of rats used	Number of rats surviving	Percentage survival + *p*-aminobenzoic acid	Percentage survival Control
*carbarsone**					
1000 mg/kilo i.m.	1 gm/kilo × 6 days	10	10	100	
"	controls	10	1		10
1000 mg/kilo i.v.	1 gm/kilo × 3 days	10	8	80	
"	controls	11	1		9
1500 mg/kilo i.p.	3 gm/kilo × 3 days	15	13	87	
"	controls	15	0		0
Tryparsamide					
3000 mg/kilo oral	2 gm/kilo × 3 days	10	8	80	
"	controls	10	3		30
3200 mg/kilo i.p.	1 gm/kilo × 3 days	16	14	87	
"	controls	16	3		18
arsanilic acid					
250 mg/kilo i.p.	2 gm/kilo × 4 days	10	10	100	
"	controls	10	5		50
400 mg/kilo i.p.	2 gm/kilo × 3 days	10	10	100	
"	controls	10	0		0
acetarsone					
4000 mg/kilo oral	2 gm/kilo × 3 days	10	9	90	
"	controls	10	6		60
400 mg/kilo i.p.	2 gm/kilo × 3 days	10	7	70	
"	controls	10	0		0
400 mg/kilo i.m.	2 gm/kilo × 3 days	30	28	93	
"	controls	10	0		0

* Carbarsone was given in the form of the soluble sodium salt. Owing to the low toxicity of this drug (MLD_{50} ca. 15,000 mg/kilo) and the physical difficulties involved in introducing as much as 7.5 cc of a 20 per cent. solution into the stomach of a 100 gm rat, it has not been possible to determine whether *p*-aminobenzoic acid has any protective value when carbarsone is administered orally to this animal.

[1] With acknowledgment to Mr. Charles R. Hamilton for valued technical aid in the conduct of this work.

[2] D. D. Woods, *Brit. Jour. Exp. Path.*, 21: 74, 1940.

[3] F. R. Selbie, *Idem.*, 21: 90, 1940.

[4] J. Maier and E. Riley, *Proc. Soc. Exp. Biol. and Med.*, 50: 152, 1942.

[5] E. K. Marshall, J. T. Litchfield, Jr., and H. J. White, *Jour. Pharm. and Exp. Ther.*, 75: 89, 1942.

that *p*-aminobenzoic acid in some way protects rats against excessive doses of carbarsone. All rats were maintained on the same adequate diet.

To test the validity of these ideas, further experiments were designed with carbarsone and also with such other pentavalent arsenicals as "Tryparsamide" (sodium N. phenylglycinamide-*p*-arsonate), arsanilic acid or atoxyl (*p*-amino phenyl arsenic acid) and acetarsone (*m*-acetylamino *p*-hydroxyphenylarsonic acid). In order to subject our presumptive conclusions to the most rigorous proof, the arsenicals were administered to heterogeneous groups of rats by various routes in dosages that previous experience had shown to be well above their respective minimal lethal ranges. *p*-aminobenzoic acid in the form of its soluble sodium salt was given by various routes in dosages well below the lethal range established by Scott *et al.*[6] All surviving rats were observed for at least ten days before being discarded. Results of a few typical experiments representative of the several drugs used are given in Table 1.

Discussion

Conclusive evidence of the absence of any inhibitory action of *p*-aminobenzoic acid on the trypanocidal potency of the various arsenicals has been obtained. This evidence, together with a discussion of the theoretical implications of the finding, will be presented elsewhere. In the present communication, attention is drawn specifically to the detoxicating action of *p*-aminobenzoic acid against massive doses of the various pentavalent arsenicals used. The protective action is dramatically demonstrated within 24 hours when, as in the case of high intravenous doses of acetarsone, nearly all the control rats are already dead or *in extremis*. On lower but still relatively high doses, particularly when administered by the oral route, some control rats linger on for four or five days, an occasional rat even surviving the experiment. In the earlier stages of the experiment, all the classical signs of pentavalent arsenic poisoning in rats, namely, tremors, gyrations, head tic, incoordination and progressive emaciation, are exhibited by the controls. The number of rats receiving adequate doses of *p*-aminobenzoic acid that show these stigmata is relatively small. Furthermore, some of the treated rats that develop central nervous system disturbances are apparently relieved of their symptoms by the continued administration of *p*-aminobenzoic acid.

In addition to work on this important point, further studies now in progress are designed to determine what pathological lesions due to the arsenical drugs are inhibited by the administration of *p*-aminobenzoic acid. Additional studies of the clinical applications of these findings in man, especially in connection with the arsenical treatment of neurosyphilis, are being undertaken.

[6] C. C. Scott and E. B. Robbins, *Proc. Soc. Exp. Biol. and Med.*, 49: 184, 1942.

Summary

p-aminobenzoic acid has been found highly effective as a detoxicant for high lethal doses of carbarsone and certain other phenyl arsonates in rats.

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ADSORPTIVE FORCES ACTIVE THROUGH GLASS[1]

A major problem in parts of some oil fields is getting the remaining crude petroleum out of sands that have been water flooded. While sand adheres to water in preference to oil and oil may be driven from an oil-saturated sand by water, if considerable water is already present with the oil in the sand, the usual water drive is not effective. The problem of recovering the remaining oil requires a study of the effect of one liquid in causing a solid particle to adhere more firmly to another liquid.

That sand partly wet with water holds crude oil much more firmly than when no water is present with the oil is easily demonstrated in the laboratory with either loose sand or disks of sandstone. The phenomenon is familiar in many aspects; froth flotation, three component emulsions, the flotation of sand grains at the interface between gasoline and water and between water and air and many others. But how can it be measured quantitatively?

A number of methods were tried and discarded in preliminary work. There appears to be no way to get oil and water to lie side by side in alternate strips on the same glass surface. The method finally adopted was to have oil and water on opposite sides of a very thin glass wall. An easily measurable effect of one fluid through the glass on the other fluid was obtained for a few of dozens of fluid combinations tried.

The method used was simply to flow the oil or other fluid through a long, very thin-walled glass capillary, then repeat with water or other fluid in the water jacket outside the capillary at precisely the same temperature. The ratio of times of flow gives the ratio of the fourth powers of the radii of the capillary and hence the thickness of the adsorbed layer. The capillary tube was drawn from ordinary 8 mm tubing (the fusible type of hard glass worked best) and was about 0.8 mm diameter and a meter long with wall thickness about 0.1 mm. It was mounted vertically by means of the undrawn ends, the upper of which was provided with two scratches to define the volume flowed. 100

[1] Published by permission of the Director, Geological Survey, U. S. Department of the Interior.