CARBON TRICHLORIDE AS AN ANTHelmINTIC, AND THE RELATION OF ITS SOLUBILITY TO ANTHelmINTIC EFFICACY

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INTRODUCTION

On the basis of a very careful and extensive study of the correlation of the chemical composition and anthelmintic efficacy of a number of drugs, Caius and Mhaskar (3) arrived at the conclusion that since chloroform showed considerable anthelmintic efficacy against hookworms, some related compound with a higher halogen content might prove even more effective, the anthelmintic efficacy in the case of chloroform being correlated with its chlorine content. By a shorter and less exhaustive line of reasoning, Hall (6) derived the same conclusion from substantially the same premises and reported that carbon tetrachloride was such an anthelmintic, his paper appearing the same month that Caius and Mhaskar predicted the likelihood of a compound related to chloroform being effective against hookworms. Since chloroform (CHCl₃) and carbon tetrachloride (CCl₄) show considerable efficacy against hookworms, it seems desirable that other related compounds should be investigated.

In a study of miscellaneous anthelmintics, Hall and Shillinger (7) have tested ethylene dichloride (C₂H₄Cl₂), and find that it has some efficacy against hookworms, but less than chloroform and carbon tetrachloride. Recently Hall and Shillinger (8) have reported that tetrachloroethylene (C₂Cl₄) is apparently even more effective than carbon tetrachloride in removing hookworms, their paper covering experiments carried out subsequent to those reported in this paper and continuing the same line of investigation. The investigation reported in this paper pertains to carbon trichloride or hexachlorethane (C₂Cl₆).

Carbon trichloride occurs in the form of colorless crystals which are insoluble in water, but soluble in alcohol, ether, carbon tetrachloride, and all oils. Its insolubility in water is a conspicuous property. When 1 gram was added to 2,000 c. c. of water there was no apparent diminution in the amount of it after two months, so little went into solution. The apparent solubility was decidedly less than 1 in 10,000. Its odor is suggestive of camphor or turpentine. On theoretical grounds, certain possibilities as regards anthelmintic action might be predicted from the chemical composition and physical nature of this substance. From its atomic structure one might conclude that it would be less effective than carbon tetrachloride, since its proportion of chlorine to carbon is 3 : 1 instead of 4 : 1. However, since the molecule actually contains more chlorine (6 atoms) than does carbon tetrachloride (4 atoms), it might prove actually more effective. Actual test throws no light on this subject of chlorine content versus chlorine concentration, for the decisive factor in connection with its internal action is the physical factor of solubility.

Anthelmintics have long been regarded as relatively insoluble, more or less toxic, substances, which, by virtue of their relative insolubility, would remain in the digestive tract to a great extent and poison the worms present, the host meanwhile absorbing very little of the poison and the drug being swept out of the digestive tract by means of a purge as soon as feasible. However, Hall (6) has noted as a principle of anthelmintic medication that "anthelmintics of the supposedly insoluble type are not as insoluble as they are commonly supposed to be," and cites the findings of Seidell in regard to thymol, to the effect that "of the thymol administered, from one-half to two-thirds is apparently destroyed or temporarily fixed in the body." Thymol, we may recall, is soluble about 1 part in 1,100 parts of water at 25° C. Carbon tetrachloride is soluble 1 part in 1,250 parts of water at 25° C.

As carbon tetrachloride appears to be about the least water-soluble of the anthelmintics in use for hookworms,
its solubility in and absorption from the digestive tract are matters of some little interest in connection with our study of an even more insoluble chlorine compound. Hall (6) pointed out in his first paper that the safety of carbon tetrachloride appears to be correlated with its insolubility. Chopra and McVail (4) say: "Owing to its low solubility and volatility and consequently slow rate of diffusion, only small quantities are absorbed into the circulation. Large quantities can therefore be introduced into the alimentary canal without untoward effects." So far as we can judge from the available evidence, the amount of absorption of carbon tetrachloride from the digestive tract does not usually increase as the amount administered is increased, or if it does, there seems to be a compensatory elimination of the larger amounts of the drug without a concomitant and strictly proportionate increase in liver injury. Wells (11) has recently shown that a high percentage of the absorbed carbon tetrachloride is rapidly excreted in the expired air.

The experience of various workers indicates that a certain amount of drug is absorbed usually and that it causes a moderate amount of injury to the liver, this injury being rapidly and completely repaired. In fact, Bose and Mukerji (1) have reported two cases in which a levulose test of liver function before and after treatment with carbon tetrachloride showed deficiency of liver function before treatment and normal function after treatment, a thing theoretically possible where a chronic indolent pathological condition is rendered acute and stimulated to repair. When large amounts of the drug, 25 c. c. per kilo, or totals of several hundred c. c. at a time, or up to 2 liters in repeated doses, are administered to dogs, as has been done, it seems clear that if the absorption and a concomitant liver injury increased proportionately these animals would be killed in all cases, as we know that animals may be killed with therapeutic doses if conditions are such as to facilitate absorption, for instance, such conditions as appear to be present in certain cases of hemorrhagic enteritis. However, normal dogs commonly survive these heavy doses, showing that absorption or the tissue injury from the absorbed drug is limited; almost all the deaths reported in man and dogs followed therapeutic doses.

Lamson, Gardner, Gustafson, Maire, McLean and Wells (9) report that of 35 dogs given 100 to 500 times the therapeutic dose only 1 died. To put it in other words, there is no such thing as a minimum lethal dose of carbon tetrachloride for such animals as man and dog, and the same is true for chickens. Individuals of high individual intolerance for the drug may be killed with therapeutic doses, but normal individuals will tolerate enormous doses, and the limit of tolerance for normal dogs appears to be approximately the limit of gastric capacity. Chloroform, a much more soluble product, soluble 1 part in 161 parts of water at 22° C., is apparently much more readily and regularly absorbed in the digestive tract than is carbon tetrachloride, or a resultant injury is more regularly produced. Caius and Mhaskar (2) state in regard to chloroform: "Toxic symptoms are occasionally noticed with a dose of 30 minims [2 c. c.] and become more general and more marked with increasing dosages until 45 minims [3 c. c.] is reached." A dose of 3 c. c. of carbon tetrachloride is the one most used for human adults and usually causes no symptoms or only slight and transient symptoms. Much larger doses have been administered without evident bad effects. Peyre (10) has reported no inconvenience from carbon tetrachloride in a case of hepatic cirrhosis with ascites, precisely the sort of case in which bad results would follow if absorption and proportionate injury occurred to any marked extent.

Reasoning from the increased efficacy and safety of carbon tetrachloride as compared with chloroform, and associating it with its lesser water-solubility as perhaps the determining factor for these qualities, the writers have raised the question as to whether a halogen compound less soluble than carbon tetrachloride might be still more effective against hookworms, or safer, or more effective and safer. Carbon trichloride is evidently a less soluble halogen compound. The following experiments were made to test it.

**Experimental Data**

**Coarse Crystals Administered in Capsules**

Six dogs were given the coarse crystals in capsules, the number of each dog, its weight, its total dose, and its dose rate in terms of grams per kilo (g. p. k.) being as follows: Dog. No. 665, 13 kilos, 1 gm. (0.077 g. p. k.); No. 666, 10 kilos, 2 gm. (0.2 g. p. k.); No. 667, 6.5 kilos, 3 gm. (0.46 g. p. k.);
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No. 668, 9.5 kilos, 4 gm. (0.42 g. p. k.); No. 669, 7 kilos, 1 gm. (0.14 g. p. k.); No. 670, 6 kilos, 6 gm. (1 g. p. k.). These dogs had been fasted overnight previous to the morning of treatment.

The feces next day showed no worms, except 3 gravid Dipylidium segments, but all of the feces contained an abundance of the carbon trichloride crystals, the amount seen being such as to suggest that the total amount passed was practically identical with the amount administered. The crystals seemed unchanged in size, shape, and general appearance. The following day there were no worms in the feces except Dipylidium segments, and there were no crystals. Satisfied that carbon trichloride crystals alone were approximately as insoluble in the digestive tract as in water, that they passed through the digestive tract, for the most part, in the course of 24 hours, and that they did not remove worms, the theory that this oil-soluble chemical might be put in contact with worms and its anthelmintic constituent rendered available and effective by the simultaneous administration of castor oil was next tested as follows.

FINE POWDER ADMINISTERED IN CAPSULES WITH CASTOR OIL

Crystals of carbon trichloride were finely powdered in a mortar and administered in capsules, this dose being immediately preceded or followed by 1 ounce of castor oil. The number of each dog, its weight, and its total dose were as follows: Dog No. 680, 7 kilos, 5 gm.; No. 679, 7 kilos, 6 gm.; No. 678, 8 kilos, 7 gm.; No. 683, 10.5 kilos, 8 gm.; No. 682, 9 kilos, 9 gm.; No. 681, 9 kilos, 10 gm. The following day the finely powdered carbon trichloride was visible in the feces. Dog No. 679 passed 1 whipworm the next day and 2 whipworms the day after, a total of 3 whipworms, and No. 680 passed a hookworm the day after treatment. No other worms were passed the fourth day, and on that day the dogs were killed and examined post-mortem. The worms present post-mortem were as follows: Dog No. 680, 35 hookworms; No. 679, 24 whipworms; No. 678, 5 hookworms, 16 whipworms; No. 683, 25 hookworms, 75 whipworms, 1 Dipylidium; No. 682, 1 hookworm and 1 whipworm; No. 681, negative. Dog 679 passed 3 whipworms and had 24 left; there were 92 whipworms left in the other dogs. Dog 680 passed 1 hookworm and had 35 left; there were 31 hookworms left in other dogs. This experiment suggests that the finely powdered carbon trichloride in the presence of castor oil may become slightly effective against worms, but it indicates that the chemical would probably never be of value as an anthelmintic. To give this feature of oil solubility a more definite test, we tried the carbon trichloride in oil as follows.

CARBON TRICHLORIDE DISSOLVED IN CASTOR OIL

One gram of carbon trichloride was dissolved in 100 c. c. of castor oil with the aid of moderate heat, the solution becoming a brownish amber color. The entire amount was given by drench to dog No. 669. This animal passed no worms the next day, passed 7 whipworms the next day, none the next 2 days, and on post-mortem examination the fourth day after treatment had 14 hookworms, 18 whipworms and 40 to 50 tapeworm heads. The treatment appears to have removed 28 per cent of the whipworms. While little can be concluded from the foregoing experiments as to the effects of oil on the availability of the anthelmintic constituents of the chemical, the results suggest that this highly insoluble drug is entirely ineffective and unavailable when given alone as coarse crystals; that it becomes slightly effective and available when given as a fine powder accompanied by castor oil; and that it becomes still more effective, though by no means really valuable, when it is dissolved in oil and then administered.

Since the efficacy of oil of Chenopodium for removing worms from dogs is fairly well known from large numbers of critical experiments, the writers next undertook to test the efficacy of carbon trichloride dissolved in this oil. The oil alone falls distinctly short of 100 per cent efficacy against hookworms in dogs, so that any marked increase in efficacy on the part of the mixture might be detected and would indicate an anthelmintic action on the part of the carbon trichloride.

CARBON TRICHLORIDE DISSOLVED IN OIL OF CHENOPODIUM

Six grams of carbon trichloride were dissolved in 20 c. c. of oil of Chenopodium, without heat, and the dose rate for Chenopodium for removing hookworms was used for the mixture in treating 6 dogs. This dose rate is 2 c. c. for dogs of average size or larger, and 1 c. c. for small dogs. Two c. c. was given to dogs No. 672 (14 k.) and 673 (12 k.), and 1 c. c. was given to
dogs No. 674 (6 k.), 675 (6.5 k.), 676 (6.5 k.), and 677 (6.5 k.). One ounce of castor oil was given at the same time. The worms passed during the next 4 days, those present post-mortem, and the percentage of efficacy were as follows:

Dog 672 passed 7 hookworms and had 3 post-mortem (70 per cent), passed 27 whipworms and had 1 post-mortem (96 per cent), passed 0 Dipylidium and had 17 post-mortem (0 per cent).

Dog 673 passed 0 hookworms and had 2 post-mortem (0 per cent), passed 2 whipworms and had 26 post-mortem (7 per cent), and passed 0 Dipylidium and had 8 post-mortem (0 per cent).

Dog 674 passed 7 hookworms and had 3 post-mortem (70 per cent), passed 27 whipworms and had 1 post-mortem (96 per cent), passed 0 Dipylidium and had 17 post-mortem (0 per cent).

Dog 675 passed 0 worms and had 1 hookworm, 17 whipworms and 1 Dipylidium sp., an efficacy of 0 per cent for hookworms, whipworms, and Dipylidium.

Dog 676 passed 0 worms and had 4 whipworms post-mortem; efficacy 0 per cent for whipworms.

Dog 677 passed 0 hookworm and had 0 post-mortem (100 per cent), passed 1 hookworm and had 1 post-mortem (50 per cent), and passed 1 whipworm and had 0 post-mortem (100 per cent).

The protocols were as follows:

Dog 665: 0.3 c. c. per kilo of solution in capsules; passed 2 hookworms, 10 ascarids, and 16 whipworms; post-mortem, 4 whipworms; efficacy, 100 per cent for hookworms and ascarids, and 80 per cent for whipworms.

Dog 666: 0.3 c. c. per kilo in capsules; passed 1 hookworm and 4 whipworms; post-mortem, 5 whipworms; efficacy, 100 per cent for hookworms and whipworms.

Dog 667: 0.5 c. c. per kilo by capsule; passed 1 whipworm; post-mortem, 0 worms; efficacy, 100 per cent for whipworms.

Dog 668: 1 c. c. per kilo by stomach tube; passed 2 hookworms and 15 whipworms; post-mortem, 0 worms; efficacy, 100 per cent for hookworms and whipworms.

Dog 670: 2 c. c. per kilo by stomach tube; passed 20 hookworms and 4 whipworms; post-mortem, 0 worms; efficacy, 100 per cent for hookworms and whipworms.

The solution of carbon trichloride in carbon tetrachloride was 100 per cent effective against ascarids in the 1 case involved, 100 per cent effective against hookworms in the 4 cases involved, and 100, 100, 80, and 44 per cent effective against whipworms in the 4 cases involved. At the dose rate, which is equivalent to the therapeutic dose rate for carbon tetrachloride (0.3 c. c. per kilo), the solution removed all the ascarids and hookworms and 44 and 80 per cent of the whipworms. This is just about what would be expected from the carbon tetrachloride alone. In the higher rates the efficacy against whipworms rises, as it should theoretically, and as it does frequently in actual practice. Apparently the addition of the carbon trichloride to the carbon tetrachloride does not add to or detract from the anthelmintic efficacy of the latter chemical.

**PATHOLOGY**

In order to obtain additional information, if possible, in regard to the solubility of carbon trichloride and also its possible toxic effects, portions of the liver and kidneys of dogs Nos. 665, 666, 667, 668, and 670 (receiving carbon-trichloride crystals and afterwards carbon trichloride in carbon tetrachloride), and of No. 669 (receiving carbon-trichloride crystals and afterwards carbon trichloride dissolved in castor oil), were submitted to the Pathological Division, Bureau of Animal Industry, for examination. These tissues were examined by G. T. Creech, who reported that he found in all of them lesions similar to those which have been described by various writers as following the administration of carbon tetrachloride. In the livers there was more or less capillary congestion and the cells showed alterations varying from cloudy swelling to complete degeneration and atrophy of the cells. The kidneys showed hemorrhages, especially in the cortical por-
increasing solubility, the efficacy decreases as the solubility increases, it does not appear to promise anything of valuable in the way of anthelmintic discovery to investigate chlorine compounds of these series which are more soluble than 1 : 1,250, although such investigations have considerable theoretical interest. The anthelmintic efficacy falls to practically zero on the side of decreased solubility for the highly insoluble carbon trichloride. There is still the possibility that a chlorine compound having approximately the same chlorine content as carbon tetrachloride, but slightly less soluble, might be safer if not more effective. Tetra-chlorethylene may be such a drug. Evidently carbon trichloride is too far in the direction of insolubility. Judging from these experiments, carbon trichloride is so insoluble that its theoretically effective chlorine content is unavailable and ineffective.

LITERATURE CITED


