Toxicological aspects of male antifertility α-chlorohydrins

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In recent years two simple α-chlorohydrins have been considered as possible non-steroidal male contraceptives since they render morphologically mature spermatoza in the epididymis incapable of fertilizing. Apart from toxicity these substances possess most of the desirable attributes of an oral contraceptive.

α-Chlorohydrin (3-chloro-1,2-propanediol) came first but was soon rejected on account of reported bone marrow damage and other toxicity in Rhesus monkeys (Kirtin, Ericsson, Ray & Forbes, 1970). Nevertheless, much basic work continued using this liquid regarding its metabolism and mode of action, with the later discovery (Mohri, Suter, Brown-Woodman, White & Ridley, 1975) that the mode of action probably involved inhibition of certain glycolytic enzymes by the phosphorylated compound, i.e. the 1-phosphate, in sperm of susceptible animals (rat, boar, ram, guinea-pig, hamster and Rhesus monkey).

Meantime, the 1-amino analogue (1-amino-3-chloro-2-propanol) was reported to have promising contraceptive activity in rats; furthermore the desired activity was found to be associated solely with the S(−)-stereo-isomer (Coppola & Saldarini, 1974) which also appeared to be much less toxic than the inactive isomer in the rat. In our strain of rat however, this contraceptive isomer proved to be less effective than racemic α-chlorohydrin (Jones & Jackson, 1976). No data appears to have been published on the metabolism and mode of action of the amino-chlorohydrin which, unfortunately, was neuro-toxic in the Rhesus monkey.

The synthesis and antifertility potential of the two stereo-isomers of α-chlorohydrin has now been reported (Jackson & Robinson, 1976; Jackson, Fitzpatrick, Rooney & Gibson, 1977). Here also, the activity was restricted to the S(+)-isomer which was also less toxic than the R(−) compound on an LD_{50} basis. A study of the absolute spatial configuration of the S(+)-α-chlorohydrin and the S(−)-amino-α-chlorohydrin has shown that these are identical (Robinson, 1976). The mode of action of the amino-compound is yet a matter for speculation.

In the numerous publications dealing with the biological activity of racemic α-chlorohydrin there have been no data concerning the purity of the material used. Most have utilized the commercially available product; occasionally prior distillation for purification has been reported. Using the latter material we have attempted to induce bone marrow damage in mature male rats by prolonged daily oral administration (5 days per week) at 50 mg/kg, i.e. about 50% of the LD_{30} dose. All survived the treatment period of 1 year (20 animals) and 15 were still alive at 2 years from the first dose, so there was no indication of a cumulative toxic effect. This racemic compound produces infertility in laboratory rats at daily dose levels of 5–10 mg/kg oral. From the pharmacological point of view, this substance is only 50% pure and it would obviously be very desirable to use the pure synthetic (S+)-isomer for toxicity studies since this is active at 2.5 mg/kg daily. Pending its availability on the scale required, a tolerance study is in progress with beagles using doubly-distilled, fractionated racemic α-chlorohydrin. This experiment was undertaken following a report (Dixit, Lohiya & Agrawal, 1975) that daily subcutaneous doses (8 mg/kg) of α-chlorohydrin for 30 days to dogs produced inhibition of spermatogenesis and aspermia. So far, we have administered the compound orally to 3 dogs (7 days per week), 50 doses at 30 mg/kg followed by 50 doses at 60 mg/kg, without apparent adverse effect. Since the route of administration was different, it is relevant to note that in the rat racemic α-chlorohydrin shows comparable acute toxicity by both oral and subcutaneous routes. The implications of these results will be discussed.

References

COPPOLA, J.A. & SALDARINI, R.J. (1974). A new, orally active male antifertility agent (L-1-amino-3-chloro-2-propanol hydrochloride). *Contraception*, **9**, 459–470.

DIXIT, V.P., LOHIYA, N.K. & AGRAWAL, M. (1975). Effects of α-chlorohydrin on the testis and epididymides of dog: A preliminary study. *Fertil. Steril.*, **26**, 781–785.

JACKSON, H., FITZPATRICK, R.W., ROONEY, F. & GIBSON, K.H. (1977). Characterization and antifertility activity in rats of S(+) α-chlorohydrin. *Chem.-Biol. Interact.*, **17**, 117–120.

JACKSON, H. & ROBINSON, B. (1976). The antifertility effects of α-chlorohydrins and their stereo-isomers in male rats. *Chem.-Biol. Interact.*, **13**, 193–197.

JONES, PAMELA & JACKSON, H. (1976). Antifertility and dominant lethal mutation studies in male rats with *dl*-α-chlorohydrin and an amino-analogue. *Contraception*, **13**, 639–646.

KIRTON, K.T., ERICSSON, R.J., RAY, J.A. & FORBES, A.D. (1970). Male antifertility compounds: efficacy of U-5897 in primates (*Macaca mulatta*). *J. Reprod. Fert.*, **21**, 275–278.

MOHRI, H., SUTER, D.A.I., BROWN-WOODMAN, P.D.C., WHITE, I.G. & RIDLEY, D.D. (1975). Identification of the biochemical lesion produced in spermatoza by the male antifertility agent α-chlorohydrin. *Nature, Lond.*, **255**, 75–77.

ROBINSON, B. (1976). Absolute configuration of (+)- and (−)-1-amino-3-chloropropane-2-ol hydrochlorides. *Chem. Ind.*, **7**, 652.