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Sex difference in murine sensitivity to several nitrogen mustards

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IN THE course of study of the protective effect of the mercaptoalkylamines against nitrogen mustard,¹ consistent sex differences in protection were observed. Further evaluation of our data suggested that these differences actually resulted from an underlying sex difference in murine sensitivity to several alkylating agents. To test this possibility, dose-per cent effect curves were obtained for four nitrogen mustards: HN₂ (nitrogen mustard), CQM (chloroquine mustard), PAM (L-phenylalanine mustard), and CTX (cyclophosphamide mustard). The toxicity tests were performed on DBA/2 \times C3H F₁ hybrid mice,² with single doses of drug administered i.p. in 0.5 ml of 0.15 M NaCl. Dose-response curves were based on at least two experiments, involving 5 doses each and using 10 male or female mice weighing 20 ± 2 g. Results were scored after 30 days.

Data showing the ED₁₆, ED₅₀, and ED₈₄ values, as well as the 5% confidence limits for the ED₅₀ values, are given in Table 1. The ED values were obtained by means of a log-probit plot (Codex 3128 log-probability paper) according to the method of Litchfield and Wilcoxon;³ analyses for homogeneity, parallelism, and potency differences were also performed according to the procedures described by these authors. The data were homogeneous and did not depart from parallelism for the four pairs of male-female dose-response curves.

Although Table 1 shows that at all levels male animals are more sensitive to β -chloroethyl alkylating agents, only with PAM and CTX are these differences significant. Accordingly, the potency ratio (PR) and its 5% confidence limits were calculated,³ along with similar data for the slopes (SR) of the dose-response curve. The data of Table 2 show that at its upper and lower confidence limits (5%), CTX is 1.5-1 times as toxic to males as to females; for PAM the relative potency for males ranges from 2.10-1.10 times that for females.

TABLE 1. SEX DIFFERENCES IN *N*-MUSTARD TOXICITY*

| | | Dose-per cent effect relations† | | | ♂-♀ Difference‡ |
|-----------------|-----|---------------------------------|-----------------------------|--|--------------------|
| | | ED ₁₆ | ED ₈₄ (mg/kg) | ED ₅₀ (±5% confidence limits)† | |
| HN ₂ | 100 | 2.7 | 4.2 | 3.3 (2.8- 4.1) | NS |
| | | 2.8 | 4.4 | 3.6 (2.9- 4.3) | |
| CQM | 100 | 4.0 | 7.1 | 5.4 (4.4- 6.7) | NS |
| | | 4.6 | 7.2 | 5.8 (4.8- 6.9) | |
| CTX | 300 | | 440 | 370 (320-420) | S |
| | | 360 | 580 | 460 (410-520) | |
| PAM | 100 | 9.2 | 14.0 | 11.5 (9.3- 14.4) | S |
| | | 12.5 | 24.5 | 17.5 (13.8- 22.4) | |

* 20 ± 2 g DBA/2 × C3H F₁ hybrid ♂ or ♀ mice. See text for experimental details.

† Derived from log-probit plot, using method of Ref. 3.

‡ NS = not significant at 5% confidence level;

S = significant difference in potency at 5% confidence level.

TABLE 2. STATISTICAL DATA ON SEX DIFFERENCE IN RELATIVE POTENCY OF CTX AND PAM

| | CTX | PAM |
|---------------------------------|-------------|-------------|
| 1. PR | 1.24 | 1.52 |
| 2. f_{PR} | 1.20 | 1.39 |
| 3. Significance | S | S |
| 4. Relative potency at 5% limit | 1.49-1.03 | 2.11-1.10 |
| 5. SR | 1.07 | 1.14 |
| 6. f_{SR} | 1.14 | 1.36 |
| 7. Slope relation | Parallel | Parallel |
| 8. Slope ratio, 5% limits | (1.22-0.94) | (1.56-0.83) |

1. Potency ratio of ED₅₀ values.
2. Factor estimating significance of difference in dose parameter according to Ref. 3.
3. If $PR > f_{PR}$, potency difference significant (S) at 5% confidence level.³
4. Upper and lower 5% confidence limits of potency ratio = $PR \times f_{PR}$ and PR/f_{PR} .³
5. Ratio of dose-effect slopes.
6. Factor estimating significance of difference in slope.³
7. If $SR < f_{SR}$, lines parallel.³
8. $SR \times f_{SR}$ to SR/f_{SR} .

Although sex differences in sensitivity to ionizing radiation are known,⁴ it is believed that this is the first report of such a difference for alkylating agents. The magnitude of the differences is equal to or greater than that reported for radiation.

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