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JOURNAL ARTICLE

Long-term effects of triptolide on spermatogenesis, epididymal sperm function, and fertility in male rats

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Prior studies had suggested that triptolide, a diterpene triepoxide isolated from a Chinese medicinal plant, might be an attractive candidate as a post-testicular male contraceptive agent. Despite the promise that triptolide would not affect testis function, nagging concerns remained that a delayed onset of testicular effect might exist. The objectives of this study were to assess the effects of relatively longer treatment duration of triptolide on fertility, spermatogenesis, and epididymal sperm pathophysiology; and to evaluate the reversibility of these effects after the cessation of treatment. Adult male Sprague-Dawley rats were fed daily with either 30% gum acacia as a vehicle control (n = 12) or 100 microg/kg body weight (BW) of triptolide for 82 days (n = 12) followed by a recovery period of up to 14 weeks (n = 6). At the end of the treatment period, all rats treated with triptolide were sterile. Cauda epididymal sperm content decreased by 84.8% and sperm motility was reduced to zero. In addition, virtually all cauda epididymal sperm in the triptolide-treated group exhibited severe structural abnormalities. The most striking changes observed were head-tail separation, premature chromatin decondensation of sperm nuclei, a complete absence of the plasma membrane of the entire middle and principle pieces, disorganization of the mitochondrial sheath, and aggregation of many sperm tails. Longer treatment duration of triptolide also affected spermatogenesis, with marked variability in the response of individual animals. The degree of damage ranged from apparently normal-looking seminiferous tubules to flattened seminiferous epithelium lined by a single layer of cells consisting of Sertoli cells and a few spermatogonia. Affected tubules exhibited intraepithelial vacuoles of varying sizes, multinucleated giant cells, germ cell exfoliation, and tubular atrophy. Recovery occurred as early as 6 weeks after cessation of treatment. By 14 weeks, 4 out of 6 triptolide-treated males were fertile and the females that were impregnated by 3 out of 4 triptolide-treated male rats produced apparently normal litters. These results suggest that triptolide has 2 phenotypic effects on mature and maturing germ cells. The first action appears earlier and manifests mainly in epididymal sperm. The second action presumably is directly on germ cells in testis and causes a variable impairment of spermatogenesis that may not be completely reversible. It is unclear if the earlier effect is a delayed manifestation of subtle testicular injury or post-testicular action.

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