Dacarbazine induces genotoxic and cytotoxic germ cell damage with concomitant decrease in testosterone and increase in lactate dehydrogenase concentration in the testis

Abstract

Treatment of cancers with cytotoxic agents such as alkylating drugs often, but not always results in transient to permanent testicular dysfunction. The present study was planned to investigate the effects of dacarbazine [5-(3,3-dimethyltriazeno) imidazole-4-carboxamide] on testicular function in mice. Swiss albino mice (9-12 weeks old) were treated with 0, 5, 25, 50, or 100 mg/kg body weight/day dacarbazine (i.p.) for 5 days at intervals of 24 h between treatments. Mice were sacrificed on days 7, 14, 21, 28, 35, 49, and 70 after the last treatment (6 mice/dose/sample time), and the epididymal sperm count, sperm motility, sperm morphology, testicular histopathology (qualitative histopathology, seminiferous tubular diameter and epithelial height), and intra-testicular levels of testosterone and lactate dehydrogenase were assessed. Dacarbazine decreased the body weight only on day 28 at 25 mg/kg dose-level, but increased the paired testes weights at 50 mg/kg on day 7, at 25-100 mg/kg on day 14, and at 25 and 50 mg/kg on day 21 (P < 0.05-0.01; one-way ANOVA and Bonferroni’s post hoc test). The sperm count was decreased on all sampling days except at 5 and 25 mg/kg dose-levels on day 70, but with severe oligospermia on days 28 and 35 (P < 0.05-0.001). The sperm motility was decreased at 100 mg/kg on days 14 and 21, at 5, 25, and 100 mg/kg on day 28, and at all dose-levels on day 35 (P < 0.05-0.001). Dacarbazine induced both head and tail abnormalities and some sperms with cytoplasmic droplets, but significant increase was seen in all dose groups on days 14 and 21, and at 100 mg/kg dose-level on day 35. Drug-induced epithelial sloughing was seen on days 14-35 and other histopathological changes observed were vacuoles and abnormal cells. The STD was increased at 25-100 mg/kg on day 7, at all dose-levels on day 14, at 50-100 mg/kg on days 21 and 28, but without any effects on days 35-70 (P < 0.05-0.001), and the tubular lumen was found dilated. The SE was increased on days 7, 21 and 28 at 100 mg/kg and on day 14 at 50-100 mg/kg.
Dacarbazine reduced the intra-testicular testosterone level at 100 mg/kg on day 7, at 5, 50 and 100 mg/kg on day 14, at all dose-levels on days 21, 28, and 35, and at 50 mg/kg on day 49 (P < 0.05-0.001). The intra-testicular lactate dehydrogenase concentration increased at all dose-levels up to day 35, but without any effect on days 49 and 70 (P < 0.05-0.001). There was no particular dose-response of dacarbazine on any parameters tested. The sperm count (except on day 7-positive correlation; Pearson product moment correlation) or sperm motility did not have any relation but increase in abnormal sperms showed negative correlation with decrease in testosterone level on days 7, 21 and 28. Decrease in sperm count was in negative correlation on days 14 and 35, and increase in abnormal sperms showed positive correlation on day 35 with increase in LDH level. Finally, the decrease in sperm motility had no correlation with increase in abnormal sperm shapes. We conclude that dacarbazine is genotoxic and cytotoxic to the mouse testis in a transient fashion, and these effects are exerted along with decrease in testosterone and increase in lactate dehydrogenase levels in the testis. (c) 2006 Elsevier B.V. All rights reserved.