COLCHICINE AND TESTICULAR FUNCTION IN MAN

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COLCHICINE, used for centuries in the therapy of gout,[1] has recently been shown to be beneficial in the prevention of attacks of familial Mediterranean fever.[2,3] Reports of a toxic effect of colchicine in sperm production in man[4] and laboratory animals[5] have appeared and have led to recommendations for caution in its use in males in the reproductive age group. Although gout is predominantly a disease of males, no systematic study of the effect of colchicine on testicular function in man has been reported; such a study is described in the present paper.

STUDY PROTOCOL

Seven normal men, 20 to 25 years of age, were selected. Normality was confirmed in each case by complete medical history, physical examination, urinalysis, complete blood counts and blood chemical tests. The subjects were fully informed, paid volunteers.

All subjects underwent two months of control observations. Three subjects then received colchicine for six months, followed by a further two months of control observations. Four subjects received colchicine for three to four months with no post-drug control observations. During each month of the study, whether or not the subject was receiving colchicine, he submitted three seminal fluids and had at least one peripheral venous blood obtained for measurement of luteinizing hormone, follicle-stimulating hormone and, in some months, testosterone.

Table 1. Hormonal and Sperm-Count Data (Means±S.E.M.) for Four Subjects during Two Months of Control Period and Three to Four Months of Colchicine Administration.

DATUM	CONTROL PERIOD	COLCHICINE ADMINISTRATION
Sperm count (million/ml)	81.2±9.2 (27)*	92.3±8.9 (46)
Testosterone (μg/100 ml)	0.47±0.04 (8)	0.48±0.04 (12)
LH (mIU/ml)	12.3±1.6 (11)	14.3±1.2 (16)
FSH (ng/ml)	123.6±12.3 (11)	136.9±11.2 (16)

*Figures in parentheses represent no. of measurements from which means & standard errors were calculated.

In all subjects, colchicine (Eli Lilly) was begun in a dosage of 0.6 mg per day given by mouth. It was increased over two weeks to a dosage of 2.4 mg per day. In the subjects treated for six months, this dosage was maintained for the full period of observation. Two of the subjects treated for three to four months were unable to tolerate the full colchicine dosage because of the development of diarrhea. These two subjects were maintained on a dosage of 1.8 mg per day. The subjects and the investigators were aware when the drug was being administered and in what dosages.

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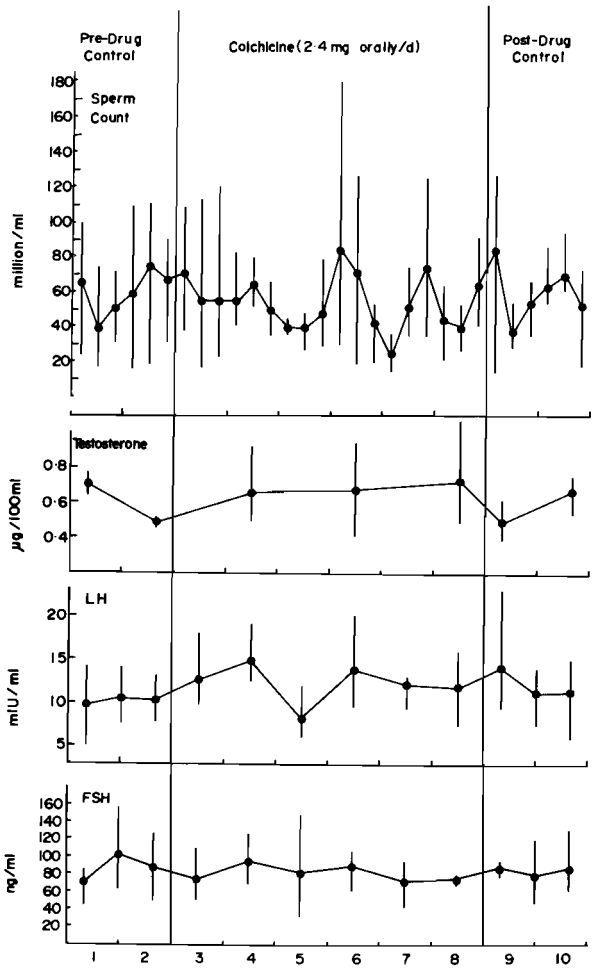

Figure 1. Hormonal and Sperm-Count Data (Means and Ranges) for Three Subjects before, during and after Colchicine Administration for Six Months (LH Represents Luteinizing Hormone, and FSH Follicle-Stimulating Hormone).

Seminal fluids were obtained by masturbation at least 48 hours after the previous ejaculation. Sperm counts were measured by Coulter counter.[6] Luteinizing hormone, follicle-stimulating hormone and testosterone were measured by radioimmunoassays.[7-9] Statistical analysis included two-way (subjects and treatment/control) analysis of variance and t-tests, for both individuals and grouped means. In the t-tests, pre-drug and post-drug control periods were compared with data from both the first and the second three-month treatment periods.

Results and Discussion

Colchicine administration caused no statistically significant changes in any of the variables measured when ingested either for three to four months (Table 1) or six months (Fig. 1). Analysis of variance revealed significant subject effects for all four variables measured ($P<0.05$), but no significant effect of colchicine administration ($P>0.05$). Of the 137 t-tests performed, three were significant at the $P<0.05$ level or less. This frequency could be expected on the basis of random occurrence, and is not considered to represent a drug effect.

One gouty patient has been described[4] in whom azoospermia appeared to be induced on two separate occasions by the consumption of colchicine in a dosage of 1.2 mg per day. Since our results demonstrated that colchicine did not depress sperm counts in normal subjects, we wondered whether gout might be associated with an increased susceptibility to a toxic effect on the testis. That this is not a universal problem in gouty patients was revealed by our study of one such subject (Bremner WJ: unpublished data) who was chronically receiving 1.2 mg of colchicine per day by mouth and who demonstrated consistently normal sperm counts. Similarly, male patients with gout receiving colchicine have been reported to be fertile.[10]

Colchicine has been reported to lead to azoospermia in hamsters and mice.[5] The dosage of colchicine used in these animals was 1.2 µg per gram of body weight per day subcutaneously. A similar dosage in a human being would be about 80 mg per day. Details of toxicity to other organ systems were not given.

No evidence was found in the present study to compel reluctance in administering colchicine, in the dosages commonly used, to men who demonstrate normal hepatic and renal function. Nevertheless, it is possible that some men are unusually sensitive to a toxic effect of colchicine on the testis.[4] If infertility is a problem in a man ingesting this compound, seminal-fluid analysis and cessation of colchicine therapy should be considered.

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