

The effect of colchicine treatment on sperm production and function: a review

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Colchicine is used for the treatment of various diseases including gouty arthritis, familial Mediterranean fever (FMF) and Behcet's disease. As a modulator of the microtubules at the cytoskeleton level, it arrests cell division at metaphase and inhibits microtubular-dependent cell motility. Controversy exists as to the adverse effect of colchicine on sperm production and function in healthy subjects as well as in gout, FMF and Behcet's patients. Sperm analysis shows a spectrum of pathology, from oligo- and azoospermia to normospermia with disturbances in sperm motility. These inconsistent sperm pathologies can be explained in part by the variability of the pathophysiology of the underlying disease. Thus, it seems that colchicine by itself may not have a significant direct adverse effect on sperm production and function.

Key words: azoospermia/Behcet's disease/colchicine/gout/oligozoospermia/recurrent polyserositis

Introduction

Colchicine is an alkaloid which has long been used for the treatment of acute gouty arthritis and for the prophylaxis of recurrent attacks of gout. Lately, it has been effectively employed for the prevention of recurrent polyserositis (familial Mediterranean fever; FMF), as well as in Behcet's disease, psoriatic arthritis, primary biliary cirrhosis and alcoholic cirrhosis (Ben-Chetrit *et al.*, 1993).

Colchicine exerts its main effect at the cellular level by its interaction with tubulin at the microtubules, inhibiting the motility and exocytosis of cellular granules. Recently it was reported that colchicine may also decrease the expression of adhesion molecules on the surface of neutrophils and endothelial cells (Molad *et al.*, 1992). Thus, the anti-inflammatory effect of colchicine is probably due to its inhibitory effect on leukocyte chemotaxis (Phelps, 1970).

Colchicine also has a powerful anti-mitotic effect. It causes metaphase arrest in cells undergoing mitosis by interfering with the formation of the mitotic spindle through blockade of tubulin polymerization. Removal of colchicine is followed by a prompt resumption of mitosis (Hsu and Satya-Prakash, 1985). Colchicine has also been found capable of arresting meiosis at the stages of first and second meiotic divisions in murine

spermatocytes (Liang *et al.*, 1985; Handel, 1979). Its effect on metaphase dynamics results in a shortening of the meiotic spindle, as shown by immunohistochemistry. These results were confirmed by employing anti- α tubulin antibodies, which revealed detachment of chromosomes from the meiotic spindle, identified as micronuclei under confocal microscopy (Kallio *et al.*, 1995).

The influence of colchicine on testicular function is controversial. A toxic effect on sperm production and function has been reported in laboratory animals (Handel, 1979; Russell *et al.*, 1981; Liang *et al.*, 1985; Kallio *et al.*, 1995) and in several sporadic reports in man (Ferreira and Buoniconti, 1968; Merlin, 1972; Margalioth *et al.*, 1985). Inhibition of spermatogenesis could originate from its anti-mitotic and anti-meiotic effects, resulting in spermatogenic arrest and azoospermia. Intratesticular colchicine injection of mice was found to cause microtubular damage and sperm abnormalities (Handel, 1979). Arrest of germ cell mitosis and meiosis accompanied by damage to the microtubular system within Sertoli cells were also shown in rats following intratesticular colchicine injection (Russell *et al.*, 1981). However, it should be emphasized that the colchicine dosages used in the animal studies were 30–50 times higher than the conventional dose, prescribed for gout or FMF patients (Bremmer and Paulsen, 1976). Based upon those data, we have reviewed the English medical literature regarding the effect of colchicine on sperm production and function in healthy individuals as well as in patients with gout, FMF and Behcet's disease. We used the MEDLINE literature search system employing the key words: 'colchicine', 'spermatozoa', 'oligo-azoospermia', 'periodic disease' and 'amyloidosis'. All papers published from 1966 to April 1997 were eligible for this review.

Colchicine effect on spermatozoa in human healthy subjects

In a prospective study of seven healthy male volunteers who received colchicine for 4–6 months, Bremmer and Paulsen (1976) were unable to demonstrate any change in sperm quality. Furthermore, serum concentrations of testosterone, luteinizing hormone (LH) and follicle stimulating hormone (FSH) were also normal. They concluded that colchicine does not affect spermatogenesis.

Since sperm motility and ovum penetration depend upon microtubular function, it is conceivable that colchicine may also affect sperm function. In a study where sperm samples from healthy volunteers were exposed to different concentrations of colchicine for various periods of time, a significant decrease in sperm motility was found (Ben-Chetrit *et al.*, 1993). This inhibitory effect was time- and dose-dependent.

Immotile spermatozoa in semen samples incubated with colchicine were not identified as necrospermic by eosin staining. However, the concentration of colchicine necessary to affect spermatozoa motility was 3000-fold higher than that achieved in the blood after an oral dose of 1–2 mg colchicine. Unless the testes have a special affinity for colchicine, leading to such a high local concentration, it seems that in therapeutic doses this agent does not affect sperm motility.

Colchicine effect on spermatozoa in patients with gout

The value of colchicine in preventing recurrences of acute gouty arthritis was recorded many centuries ago. It has been shown to decrease the production and release of crystal-induced chemotactic factor and lysosomal enzymes. The therapeutic efficacy of colchicine in gout is probably related to suppression of generation and discharge of chemotactic factor from the neutrophil (Yu, 1982).

Usually, fertility is not a concern for the majority of the older gouty population; however, early reports implicated colchicine use in sperm abnormalities. Azoospermia has been documented during chronic treatment of gout with colchicine (Merlin, 1972). The dose administered was 0.6 mg twice per day on an intermittent basis for 3 years. Three months following discontinuation of the drug, sperm count improved to normozoospermic levels. Azoospermia reappeared upon rechallenge (Merlin, 1972). Another report of two trisomic infants born to men with gout receiving colchicine drew much criticism (Ferreira and Buoniconti, 1968). The occurrence was advocated as being due to chance alone or as a result of the association between gout and chromosomal abnormalities (Walker, 1968; Hoefnagel, 1969). In a large study where the efficacy and adverse effects of colchicine were evaluated in 540 young patients with gout, their fertility status was found to be preserved (Yu, 1982). The patients received colchicine for ~20 years, all of them conceived children while on treatment and all the children were born healthy and normal.

Thus, apart from one clear-cut case disclosing an association between colchicine and azoospermia (Merlin, 1972), the overall impression is that this side-effect is relatively rare among patients treated with colchicine for gout.

Colchicine effect on spermatozoa in FMF patients

FMF is manifested by recurrent episodes of fever, serositis and arthritis. Symptoms usually start before the age of 20 years. Serum amyloid A (SAA) amyloidosis is one of the main complications of the disease. Continuous prophylaxis with colchicine is effective in the suppression of the attacks in most patients, as well as in the prevention of the development of amyloidosis (Ehrenfeld *et al.*, 1986; Ben-Chetrit and Levy, 1991).

Chronic administration of colchicine to patients of child-bearing age has raised concerns about the potential risk to fertility. In an early report, semen analyses of six FMF patients on long-term colchicine were found to be normal, and so were the hormonal profiles (Levy and Yaffe, 1978). Infertility was not encountered in 76 term pregnancies, in which one of

the parents was on prophylactic colchicine. In 24 of these pregnancies the treated parent was the father (Zemer *et al.*, 1980).

These reassuring results were in contrast to a case report of a normospermic patient receiving chronic colchicine maintenance of 1 mg daily for 5 years for FMF, who developed abnormal zona-free hamster egg sperm penetration assay. Six months after discontinuation of the drug the sperm penetration assay results improved and shortly afterwards the patient's wife conceived (Margalioth *et al.*, 1985). Another report of 19 male FMF patients receiving colchicine prophylaxis revealed fertility disturbances in four of them while on treatment (Ehrenfeld *et al.*, 1986). The array of sperm pathology included azoospermia in one patient only, whereas normospermia with pathological sperm penetration test of hamster zona-free ova was present in the remaining patients. It was concluded that male patients should undergo semen analysis before commencing treatment with colchicine. The authors suggested storing a frozen sperm sample for use in case of development of infertility during treatment. In our experience in taking care of more than 300 patients (~150 males) with FMF on colchicine, only two men were diagnosed with oligo- or azoospermia (unpublished data). It should be emphasized that these patients did not have amyloidosis or renal failure.

These conflicting reports may suggest that the expression of this adverse effect of colchicine in FMF patients may depend upon other predisposing factors related to the basic disease itself. Such pathology may include amyloidosis of the testes, a possible, albeit rare, complication of FMF. The association between sperm pathology and amyloidosis was suggested in a report of 11 young men with rheumatoid arthritis complicated by amyloidosis (Lazowski *et al.*, 1982). Azoospermia, oligoteratoasthenospermia and cryptozoospermia were found in seven of them. Amyloid deposits were detected on the vascular walls of the interstitial gland and the rete-testis of three patients. Recently we have encountered two patients with FMF and azoospermia; both of whom had renal amyloidosis and uraemia. Testicular biopsies from both cases disclosed amyloid deposits of the vessels.

This observation may suggest that the risk for colchicine-induced azoospermia in FMF patients with amyloidosis and/or with uraemia is higher compared to those with FMF only.

Colchicine effect on spermatozoa in patients with Behcet's disease

Behcet's disease is a multisystem disorder, characterized by ocular, mucocutaneous, articular, gastrointestinal, neurological and vascular pathology. The aetiology of the disease is unknown. Men are affected three times more frequently than women. Urogenital involvement is common and includes epididymitis, urethritis, recurrent cystitis and aphthous genital lesions. Colchicine is used for the prevention of the arthritic episodes and the ocular manifestations (Fukutani *et al.*, 1981).

In 131 Behcet's patients receiving 1 mg colchicine daily for >1 year, oligozoospermia, among other side-effects, was documented in 11 of them (Mizushima *et al.*, 1977). In an additional study, the fertility status of 31 patients with Behcet's

disease who were treated by cyclophosphamide and/or colchicine, was investigated by semen analyses and blood FSH values. The number of patients who were receiving colchicine exclusively was only six (Fukutani *et al.*, 1981). Sperm counts before commencing treatment were normal, suggesting that Behcet's disease by itself does not impair production of spermatozoa. The authors concluded that cyclophosphamide impaired spermatogenesis whereas colchicine did not. Recently, the urological status and the effect of colchicine on fertility in Behcet's patients were evaluated in 62 men (Sarica *et al.* 1995). Urogenital involvement was identified in two-thirds of the study group, epididymitis in 8% and arterial insufficiency, demonstrated by penile colour flow Doppler sonography, in 27%. In contrast to the previous report, sperm pathology was detected in a significant number of Behcet's patients receiving colchicine prophylaxis: 37% of men had oligoneospermia and 3% had azoospermia. However, the authors did not report the use of the eosin staining or the hypo-osmotic swell test in order to differentiate between viable but immotile spermatozoa and necrospermia. The daily dose of colchicine was not mentioned, but the deterioration in sperm quality accelerated with the longer use of the agent. Epididymitis and abnormal arterial blood flow were also more prevalent with advanced long-standing disease. We suggest that these manifestations may also account for the sperm pathology.

Thus we see that in colchicine-treated Behcet's disease, patients with impaired sperm production are more prevalent. A possible explanation may lie in the effect of vasculitis and epididymitis on spermatogenesis. These basic pathologies may predispose the patients to a higher risk for oligo- or azoospermia associated with colchicine administration.

Conclusions

In healthy volunteers colchicine treatment for a period of 4–6 months did not affect spermatogenesis. In gout, FMF and Behcet's disease there have been conflicting reports about the association between colchicine and oligo- or azoospermia. Our impression is that the frequency of colchicine-induced azoospermia among FMF patients is relatively low, although most of the patients are of child-bearing age. In gout, the majority of the patients are older, so it is possible that oligo- or azoospermia are neither detected nor reported, and this may explain the rarity of this adverse effect. In Behcet's disease this complication is more common. It is tempting to speculate that the basic disease for which colchicine is administered is an important contributing factor leading to oligo- or azoospermia. In contrast to gout, in Behcet's disease the high prevalence of epididymitis and vasculitis may account for the testicular pathology. The combination of these pathologies with colchicine treatment may lead to oligo- or azoospermia, whereas when the testes are uninvolved this adverse effect is rare. The major complication in FMF is amyloidosis. This process, which may also involve the testes, may mimic the vasculitic pathology of Behcet's disease and may enhance the appearance of oligo- or azoospermia in those who receive colchicine. Further studies are needed to confirm or refute this hypothesis.

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