Long term effects of cyclophosphamide on testicular function

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Abstract

Thirty men treated in childhood with cyclophosphamide for a mean of 280 days were assessed at a mean of 12-8 years after treatment for hormone concentrations and spermatogenesis. Four were azoospermic, nine oligospermic, and 17 normospermic. There was a significant inverse correlation of sperm density with cyclophosphamide dosage and duration of treatment. After a further mean follow up of 7-2 years three patients who were previously oligospermic and one who was azoospermic had normal sperm counts. All patients had normal sexual characteristics and libido. Serum androgen and prolactin concentrations did not differ significantly between patients and controls. Raised basal and stimulated follicle stimulating hormone concentrations were in keeping with impaired spermatogenesis. All patients had significantly raised luteinising hormone responses on stimulation with luteinising hormone releasing hormone. The results suggest compensated Leydig cell failure, and patients with this condition require long term evaluation of testicular function. Potential recovery of spermatogenesis with time requires appropriate counselling and contraceptive advice.

Introduction

Early controlled clinical trials showed that cyclophosphamide effectively maintained remission of the childhood nephrotic syndrome in patients who were sensitive to steroids and had frequent relapses.11 Until 1972 the gonadotoxicity of this drug was not appreciated.12 Subsequent reports, however, have suggested a significant inverse correlation of sperm density with cyclophosphamide dosage.13

In adult patients rendered azospermic by cyclophosphamide recovery of spermatogenesis has been documented for up to four years after treatment, a finding that has obvious implications for fertility counselling and contraceptive advice.1 Little information is available on the long term outcome with respect to recovery of spermatogenesis in patients who were treated with large doses of cyclophosphamide during childhood. In addition, as most childhood patients have been studied either prepubertally or in early adulthood reports on their testicular hormone and gonadotrophin concentrations have been confusing.11-12

This study correlates gonadal effects with cyclophosphamide dosage in a large, single centre study and documents any recovery of spermatogenesis in patients who were tested and reported on previously.1 In addition, the responses of the sex hormones of such patients were determined.

Patients and methods

Men who were aged 17 or older in 1983 and had been treated with cyclophosphamide for childhood nephrotic syndrome at The Hospital for Sick Children, Toronto, between 1967 and 1976 were considered eligible for this study. Of 70 such patients, 28 were unavailable, two had died in motor vehicle accidents, seven refused to participate, and 33 were included in the study. Three patients were subsequently excluded from analysis owing to chronic renal failure (two patients) or a single testis (one patient).

In the 30 remaining patients histological examination before treatment with cyclophosphamide showed minimal lesions in 27 and focal segmental glomerulosclerosis in three. They had been treated with cyclophosphamide at a dose of 2-3 mg/kg body weight/day for a mean of 280 days (range 42-556). Thirteen patients had received treatment for a year or longer. Two had undergone two courses of treatment roughly two years apart, and the sum of the two courses was used to calculate the dose of cyclophosphamide.

When reviewed in 1983 all 30 patients were well and free of oedema. The three who had focal segmental glomerulosclerosis continued to have proteinuria with no clinical evidence of nephrosis or serious renal impairment. Two of the six patients with minimal lesions who relapsed after...
Results

Of the 30 patients, four were azoospermic, nine oligospermic (sperm count <20×10^6/ml) and 17 normospermic (sperm count ≥20×10^6/ml). Table I shows the pubertal state at the time of treatment with cyclophosphamide. Although there was no significant correlation of total testicular volume with sperm density, the three groups of patients differed significantly in mean total testicular volume. The variables of sperm of lower percentage motility and a lower percentage of normal forms paralleled a decreasing sperm count, with significant differences noted between patients who were oligospermic or normospermic and the controls. A significant inverse correlation was evident between sperm density and cyclophosphamide dosage in terms of duration of treatment and total dosage (fig 1).

Ten patients had undergone a semen analysis 5-9 years previously, and the results have been reported.4 Nine of them remained in the same categories in this study (four normospermic, three azoospermic, and two oligospermic), but four had a low value, and in one case, no sperm count. This suggests that the type of treatment used for sperm density may be the most appropriate to consider for a follow-up study.

All patients had normal secondary sex characteristics with no noticeable decrease in libido and sexual function (two strong, eight moderate, and 20 occasional). Five patients were married and one, who was oligospermic (sperm density 12×10^6/ml), fathered a child.

Discussion

This study is the longest follow up of men who, with few exceptions, were treated with doses of cyclophosphamide above those currently recommended for childhood nephrosis treated for 6-12 weeks at a dose of 2-3 mg/kg body weight.25 The fact, however, that 25 (93%) of the patients with minimal lesions were still in remission two years after treatment and at the time of the present study shows the effectiveness of the regimen. Restriction of treatment with cyclophosphamide to 3 mg/kg body weight/day for eight weeks seems to have only a mild effect on spermatogenesis, but the remission rate at two years is roughly 50%.

Our single centre study emphasises the significant inverse correlation of sperm density with cyclophosphamide dosage in terms of duration of treatment and total dosage. These variables seem to be more important than the pubertal state of the subject at the time of treatment, although this remains debatable.25 None of the patients who were treated for less than 112 days (four months) and received less than 10 g (or less than 300 mg/kg body weight) of the drug had a sperm count of less than 20×10^6/ml, which is the currently accepted normal level for healthy men.26 Indeed, none of our control group had a sperm count of less than 22 million/ml. One oligospermic patient in our series, however, fathered a child, and this has also been reported by other workers.14

Although Buchanan et al4 reported recovery of spermatogenesis in half of adults up to 49 months after treatment with cyclophosphamide, there is a paucity of information on the long term outcome.

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**TABLE II—Findings in patients whose sperm counts improved with time**

<table>
<thead>
<tr>
<th>Case No</th>
<th>Age when cyclophosphamide was prescribed (yrs)</th>
<th>Total dosage (mg)</th>
<th>Previous evaluation</th>
<th>Current state</th>
<th>Sperm count (10^6/ml)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>11-7</td>
<td>9000</td>
<td>15-5</td>
<td>12</td>
<td>22-9</td>
</tr>
<tr>
<td>2</td>
<td>16-4</td>
<td>8000</td>
<td>20-8</td>
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<td>26</td>
</tr>
<tr>
<td>3</td>
<td>11-3</td>
<td>2000</td>
<td>18-7</td>
<td>12.5</td>
<td>25</td>
</tr>
<tr>
<td>4</td>
<td>17-5</td>
<td>4550</td>
<td>22-9</td>
<td>0</td>
<td>31</td>
</tr>
</tbody>
</table>

*p<0.005 v control group; ** p<0.005 v oligospermic and azoospermic groups; *** p<0.05 v control group.
This report documents considerable improvement in sperm counts in four of nine previously tested men after a further mean follow up of 7.2 years. Our findings have obvious implications for contraceptive advice and are also encouraging for those who have been treated with cyclophosphamide for conditions other than nephrosis.29

Although there appeared to be no overall significant correlation between total testicular volume and sperm density at the time of the study, azoospermic and oligospermic patients had lower mean testicular volumes than normospermic patients and adults in the published reports.23 No testicular biopsies were performed in our series but germinal cell aplasia has been well documented in patients treated with cyclophosphamide with apparently intact Leydig cells.11,12 Most testicular biopsies, however, have been done in young patients, and the obliteration of Leydig cells may be a slow, progressive phenomenon. Raised follicle stimulating hormone

**FIG 2—Response of follicle stimulating hormone concentration to intravenous injection of 100 μg luteinising hormone releasing hormone. Four azoospermic patients (●), nine oligospermic (○), 17 normospermic (□), and 18 controls (○).**

**FIG 3—Response of luteinising hormone concentration to intravenous injection of 100 μg luteinising hormone releasing hormone. Four azoospermic patients (●) nine oligospermic (○), 17 normospermic (□), and 18 controls (○).**

*p<0·01; **p<0·05.
concentrations both in the basal state and after stimulation with lutefine hormone releasing hormone suggest seminiferous tubular insufficiency. Thus the significantly raised concentrations in oligospermic and azoospermic patients are in keeping with germinal cell damage. Although the normospermic patients were classified as “normal” on the basis of their sperm counts, the significantly raised peak follicle stimulating hormone concentrations in this group also suggest that they have not escaped similar damage.

One of the most important findings of our study was the greatly exaggerated peak response of lutefine hormone on testing with lutefine hormone releasing hormone in all patients, irrespective of their sperm count. As lutefine hormone binds only to Leydig cells an exaggerated response on testing with lutefine hormone releasing hormone of normal testosterone concentrations indicates compensated Leydig cell failure. Other studies have noted raised basal lutefine hormone concentrations in some patients treated with high doses of cyclophosphamide, but evaluation has often taken place peripherally with conflicting results. Kirkland et al reported an exaggerated response of lutefine hormone to lutefine hormone releasing hormone in patients treated prepubertally or pubertally; but they did not record semen analyses. Further evaluation of the incipient Leydig cell failure suggested by these results will require the assessment of responses of testicular hormones to stimulation with human chorionic gonadotropic hormone, as our patients currently have normal secondary sex characteristics and libido with normal testosterone concentrations.

This study confirms the significant inverse correlation of cyclophosphamide dosage with its effect on spermatogenesis and documents clearly, for the first time, the long term effects on the Leydig cell component of the testis. The recovery of sperm counts in some subjects after a prolonged interval after treatment is encouraging. All patients treated with high doses of cyclophosphamide should have regular estimations of testicular hormone concentrations as Leydig cell failure may develop with time even in normospermic subjects.

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100 YEARS AGO

A certain amount of pleasure of its kind may doubtless, as stated by some authors, be derived from smoking opium. If it were not so, we should know nothing of the later and worse consequences of this practice. Such enjoyment as there is, it is true, is short-lived, and the after-effects produced by this drug, as most of those who have had occasion to use it are but too ready to admit, are sufficiently unpleasant, to say no more of them, to cure the craving of any but an eager student in experimental narcotism. It may be said that such difficulties are not insuperable. No, but they must be obviated by some system of counter-drugging, or by training the constitution by habit to bear a certain amount of the opium. But what amount? and how to bear it? These are questions which cannot be concisely answered. Quantity, in this case, comes readily to mean the measure of a constantly increasing appetite, and endurance is no other than unhealthy slavery, difficulty to escape from, and difficult to live under, which may well be said to begin in delusion, and to end, commonly, in disastrous arrest of every useful function. Something may be said for moderation in the use of alcoholic liquors or tobacco. In regard to the habitual, or even occasional, employment of opiates outside of medical practice, there is no such term as moderation. Disease is their only excuse. Their value, therefore, is purely therapeutic, and the preferable form for their administration in most cases of illness, and merely with a view to their efficiency, is not that of inhalation. We cannot have occasion to write on this subject before, and have drawn attention to dangers other than moral or mental, or such as only generally affect the physical state. The fact that persons who often know nothing, or next to nothing, about their own health, and yet are the very unfinest subjects for such a drug as opium, may freely treat themselves with it for any casual pain or worry, appears to us a yet graver source of evil. To restrict the right of sale of this poison to chemists or dispensing practitioners, and to limit the privilege allowed to them, would encroach on no public right, and would give security where now there is none. We have been led to make these observations at the present time by seeing a card of advertisement, apparently for public distribution, which intimates that an establishment, where opium-smoking is taught, will shortly be opened in the West End of London. We sincerely deprecate such arrangements, and trust that the introduction of such injurious novelties may do something to direct legal action in the way which they require. A suggestion is made that medical men should avail themselves of the opium-pipe as a therapeutic agent. We feel sure that we represent the bulk of medical opinion in repudiating this suggestion. (British Medical Journal 1885;ii:751.)

The itinerant fishmongers of Paris, in order to supply their customers with well cleaned fish, were accustomed to salt, whippings, place, etc., in the gutters, which are plentifully supplied with water. People who have the advantage of residing in the immediate vicinity of a good flowing gutter may frequently observe these sanitary precautions, and are thus forewarned and forearmed. Others, in this respect less fortunately placed, constantly purchase, in confiding innocence, fish cleaned in gutter-water flowing through Paris streets, and devour the same, prepared with that skill for which the French cook is famed, a skill which may conceal bad flavours, but cannot protect the consumer against the evil results of devouring contaminated food. (British Medical Journal 1885;ii:1124.)

References
1 Barritt TM, Soothill JF. Controlled trial of cyclophosphamide in steroid-sensitive relapsing nephrotic syndrome of childhood. Lancet 1974;i:479-82.
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