

DISCUSSION :

Indomethacin and other NSAIDs have been shown to raise mean sperm counts⁸. The indiscriminate use of In in treatment of infertile males will however result in many treatment failures. Even in our selected population, only 50% responded by a rise in sperm count. Because the major efforts of PG are in testosterone synthesis⁸, it appears rational to utilise PG synthase inhibitors in patients with low T levels.

Statistical analysis has failed to show any difference in the FSH, LH and Prolactin, EIPA and EILO levels. However, the mean levels of FSH and LH were lower in responders and none of the patients with FSH above 20 mIU/ml (upper limit of normal) responded to In. One azoospermic has also responded to therapy with In but in general oligospermics respond better. The mean T was lower (at the lower end of normal testosterone range) in responders.

EIPA and EILO did not have a predictor value. As prostaglandins are autocooids, perhaps estimation of intratesticular PGs may be more helpful.

The biphasic response seen may represent an escape from control by In.

It appears that oligospermics with low testosterone levels in the lower 1/2 of normal range or below and normal FSH levels will respond best to In therapy. Earlier studies (unpublished) have shown a group of patients with high LH levels but with T levels in the lower 1/2 (300 - 750 ng/dl) of the normal range. These patients may be having an excess of GnRH producing an adverse on T production. This has been shown to be due to PG. It may be worthwhile including this group of patients in further trials of NSAIDs.

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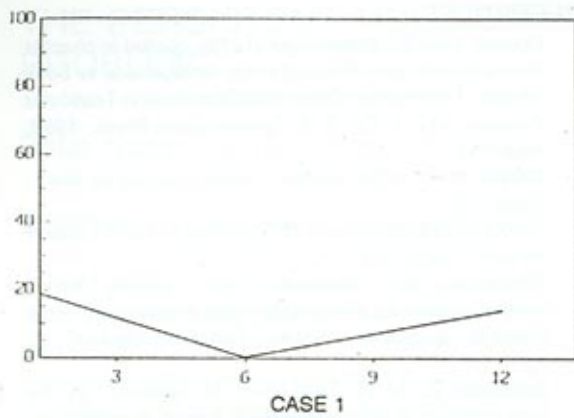


Fig. 1 Sperm Count and Motility :
Pre-treatment and six and twelve weeks after
Indomethacin-Biphasic Response.

SPERM COUNT IN MILLIONS/ml.
EIPA 9.8 % LH]
EILO 75 % PRL] Normal
FSH Elevated T]

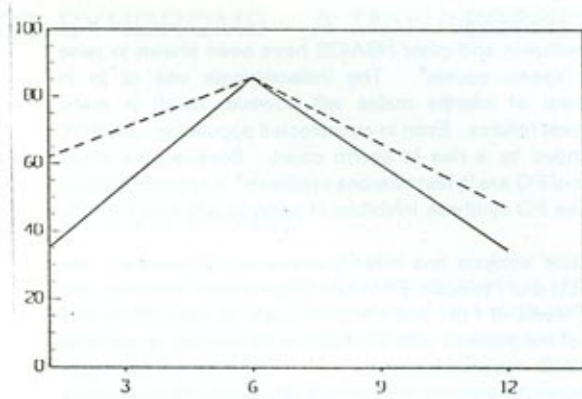


Fig. 2 CASE 2
EIPA 43 % LH]
EILO 50 % PRL] Normal
FSH Elevated T]

WEEKS AFTER TREATMENT
Interrupted lure motility. Continuous line sperm
count.

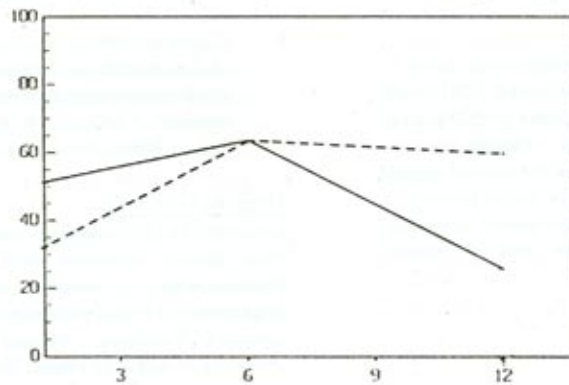


Fig. 3 CASE 3
EIPA 13.7% FSH]
EILO 62.5% LH]
FSH] PRL] Normal
T]

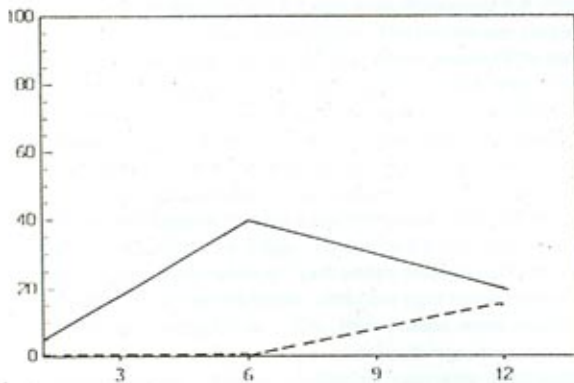


Fig. 4 CASE 4
Sperm Count and Motility :
Pre-treatment and six and twelve weeks after
indomethacin-Biphasic Response.

EIPA 39 % FSH]
EILO 66 % LH] Normal
PRL]
T Low

WEEKS AFTER TREATMENT

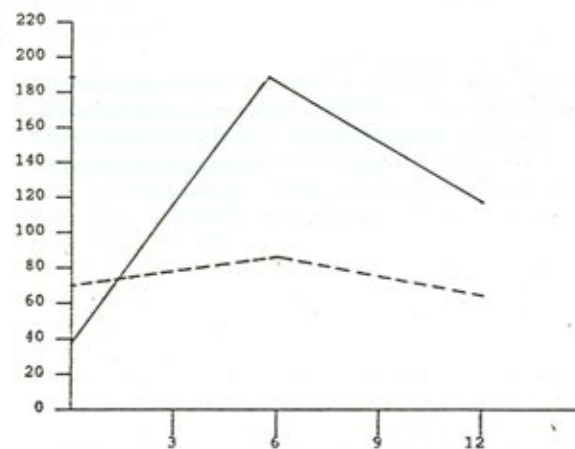


Fig. 5 CASE 5
SPERM COUNT IN MILLIONS/ml.

EIPA 33 % FSH]
EILO 78 % LH] Normal
PRL]
T Low

WEEKS AFTER TREATMENT

TABLE I

Use of Indomethacin and Aspirin in patients in whom the sperm count failed to improve three months after high ligation of testicular veins for varicocele.

Patients	Sperm Count (M/ml)		Motility (%)	
	Pretreatment	Posttreatment	Pretreatment	Posttreatment
A	10	35	Few	50%
B	30	55	20%	40%

PATIENTS AND METHODS :

Between January and September 1986, 31 patients were selected for Indomethacin (In) therapy from a large group of infertile patients who had a complete history and physical examination, estimation of follicle stimulating hormone (FSH), luteinizing hormone (LH), Prolactin (PRL), Testosterone (T) and semen analysis. Patients were excluded if they had a sperm count of over 40 million and more than 50% sperm were motile or if the patient had an overt easily treatable cause for infertility or obstructive azoospermia. However, patients with a varicocele who repeatedly refused surgery were included in the trial as also patients with low T level. The latter exception was made because we feel that NSAIDs increase Testosterone synthesis. A testicular biopsy was done to exclude obstructive azoospermia if indicated. All patients included in the trial had in addition to above mentioned tests, an estimation of endogenous inhibitors of lipoxygenase (EILO) and endogenous inhibitors of platelet aggregation (EIPA), as in earlier investigations we had noted an increase in EILO activity and decrease in EIPA activity in infertile males⁸.

Patients included in the trial were given Indomethacin 25 mg TDS for 12 weeks.

All patients were requested for a semen analysis at 6 and 12 weeks.

A 12 week follow-up is available in 21 patients.

RESULTS :

The result are tabulated in Table II. Eleven of the 21 patients showed an improved sperm count. The results were analysed to determine whether FSH, LH, PRL or T levels, presence or absence of a varicocele, levels of EIPA or EILO or sperm count could be determined or predict response to In.

TABLE II
"Response to Indomethacin"

No. of patients treated	31
3 months follow-up available	21
Improved sperm count	11 (53.4%)
Improved motility	6 (29.6%)

Table III show that azoospermics are less likely to respond than oligospermics, or patients with a low motility. Of the three patients with varicocele, 2 responded, 1 did not. The mean LH, FSH, PRL and T in responders was not statistically significantly different from that in non-responders. However, none of the patients with an FSH above 20 responded and half the patients who responded had T levels below 300 ng/dl (Table IV). Disappointingly EIPA and EILO did not appear to be predictors (Table V).

TABLE III
Pretreatment Seminal Parameters in Responders and Non Responders to Indomethacin

	Responders	Non-responders
Non-obstructive azoospermia	1	5
Oligospermia \leq 20 M/ml	5	2
Motility \leq 50%	7	4
Varicocele present in	2	1

TABLE IV
Gonadotrophin Prolactin Testosterone Levels in Responders and Non-responders to Indomethacin

	Responders (11)	Non-responders (10)
FSH	5.3 ± 3.55 SEM 1.07	15.96 ± 14.42 SEM 4.81
No. of patients with FSH > 20 mIU/ml	0	3
LH	6.08 ± 1.85 SEM 0.67	11.55 ± 8.40 SEM 2.97
PRL	8.9 ± 6.52 SEM 1.97	6.81 ± 3.51 SEM 1.17
T	399.1 ± 215.09 SEM 64.86	560.68 ± 424.07 SEM 141.35
No. of patients with T < 300 ng/dl	5	2

TABLE V
EIPA and EILO in Responders and Non-responders to Indomethacin

	Responders	Non-responders
EILO	53.57 ± 14.93 SEM 4.72	54.89 ± 18.55 SEM 5.87
EIPA	26.14 ± 9.94 SEM 3.14	22.77 ± 18.29 SEM 5.43

Biphasic Response

4 patients showed a biphasic response with the sperm count rising at 6 weeks but returning to lower levels at twelve weeks after treatment (Fig. 1 - 2). One patient dropped sperm count at 6 weeks.

INDOMETHACIN IN MALE INFERTILITY: EFFECTIVENESS AND PREDICTORS OF RESPONSE.

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ABSTRACT :

Prostaglandins (PG) inhibit testosterone synthesis and spermatogenesis. Indomethacin (a PG synthase inhibitor) has been used in male infertility but improves the sperm count in only a proportion of patients.

The present study was done to determine parameters which will predict a favourable response to Indomethacin (In). 21 infertile males were given 25 mg. In three times a day for 12 weeks. Pre and post treatment semen analysis levels were compared. Pre treatment FSH, LH and Prolactin (PRL) levels and level of Endogenous Inhibitors of Platelet Aggregation (EIPA) and endogenous inhibitors of lipooxygenase (EILO) were also determined.

In 11 (52.4%) patients sperm counts improved. 19.1% patients showed improvement at six weeks with a decline of sperm count at 12 weeks. 6 (29%) patients showed improved motility. Oligospermics responded better than azoospermics. Of the three patients with varicocele who were not treated by operation, two responded.

The mean FSH and LH were lower (and in the normal range) in the responders to In therapy. The mean T was lower (and the lower end of T range) in patients who responded. Only one azoospermic responded to therapy.

There was no statistical difference in the mean EIPA and EILO levels of responders and non-responders.

Indomethacin raised sperm counts in patients with normal FSH and LH and low T levels. EILO

and EIPA do not have predictor value. Indomethacin will be ineffective in most patients with azoospermia, and raised FSH levels. The role of In in varicocele therapy needs to be explored.

Key words : Male infertility - Indomethacin - Predictors of response - EIPA - EILO - Gonadotrophins.

INTRODUCTION :

Testicular Prostaglandins (PG) can interfere in spermatogenesis and testosterone production in a number of ways. Pharmacological amounts increase cyclic AMP, but reduce LH induced testosterone production¹.

PGs can inhibit 3 hydroxysteroid dehydrogenase² and bind cytochrome P450³ and thus inhibit testosterone synthesis.

The effect of serotonin on reducing testosterone synthesis is mediated by PG as also the direct effect of gonadotrophin releasing hormone on the testis. PG may shunt arachidonic acid (AA) away from the cytochrome P450 pathway and hence reduce T production.

Consentino et al⁴ have shown that prostaglandins are important determinants of male infertility potential and their levels are significantly interdependent with parameters of male infertility.

As PG have so many deleterious effects, it is possible that PG synthetase inhibitors will have a beneficial effect in infertile oligospermic patients. Our initial experiences with Indomethacin (In) a NSAID and PG synthase inhibitor were in the treatment of 2 patients whose sperm counts did not improve after surgery for varicocele (Table I). Both showed a dramatic improvement. Later we used In in oligospermics and noted that whilst some patients showed a dramatic increase from 0.1 to 100 million sperms/ml there were patients who did not respond.

Bendvold et al (1985) has shown that naproxen a non-steroidal anti-inflammatory drug lowers seminal PGs⁵. Used for a short time however, this drug did not alter seminal characteristics. Bendvold⁵ concluded that the ratio of 19 hydroxy PG to 19 hydroxy PG F was more important to sperm motility than a change in absolute levels of PG. Barkay et al⁶ have shown an increase in FSH levels and sperm counts motility and fertilizing capacity using indomethacin in doses of 75 mg a day for 60 days. Obviously there is a need to determine which patient will respond favourably to Indomethacin.

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