Urinary Complications Occurring During Isoniazid Treatment

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Isoniazid as a specific agent for the treatment of pulmonary tuberculosis is being increasingly used and the tendency is for it to be given to patients who for one reason or another cannot tolerate paraaminosalicylic acid. These patients are frequently in the older age group. In addition the incidence of tuberculosis is tending towards the older individuals and drugs are administered for lengthy periods. Often they are given in homes where close observation is not as easy as in sanatoria and hospitals.

Many writers state that with the conventional dosage, toxic effects are minimal or absent. This combination of older patients and longer treatment suggests that caution is desirable before assuming that the drug is innocuous. Most accounts of results in larger series of cases mention at least some urinary symptoms connected with the use of isoniazid. This report concerns four cases where during isoniazid treatment the patients developed marked edema, with rising blood N.P.N. and in three of whom there was urinary retention as a major symptom. It is possible that the use of the drug precipitated a degree of prostatic obstruction.

Case 1: This 80 year old white male was admitted to the Middlesex County Sanatorium on November 12th, 1953. The diagnosis of pulmonary tuberculosis had been made in 1951, but he had failed to avail himself of treatment. On admission the chest x-ray film showed infiltration at the right upper zone. Tubercle bacilli were demonstrated in the sputum by concentration, culture and animal inoculation. Skin test was positive using 0.1 mgs. old tuberculin. The general clinical condition was good. Mentally he was alert and took a keen interest and active part in the life of his community. Physical examination was not remarkable. The prostate was smooth, not tender, there were no nodules and it was symmetrically enlarged to about four times normal size. On particular enquiry he stated he had never had frequency, urgency, burning on micturition, difficulty in starting micturition or other symptoms suggesting prostatic obstruction. The urine was normal on chemical and microscopic examination. The dilution and concentration power showed a specific gravity ranging from 1003 to 1027.

Treatment commenced with streptomycin sulphate 1 gram twice a week, and isoniazid 200 mgms. daily in divided dosage (4 mgms. per kilo). In view of his age and the relatively indolent nature of the disease, which had remained radiologically unchanged for two years, he was allotted a modified rest regime being allowed up in his room for all toilet privileges and for meals. On this routine he remained symptom free, his weight started to increase and temperature remained within normal limits.

Six weeks after treatment started he reported slight swelling of the feet towards the end of the day. The clinical examination was normal. The urine was negative and blood pressure was not elevated. Fluid intake and output chart over a period of a week was satisfactory and no change in therapy was made.

On March 22, 1954 three months after the start of therapy, he again reported swelling of the feet and on examination there was pitting edema of the lower limbs to above the knees a.u. in the sacral area. The blood N.P.N. was 56 mgms. per cent and the urine was again normal. He now complained of slight nocturnal frequency passing small quantities of urine each time. Isoniazid was stopped and there was a slight decrease of the edema. After four days it was again administered this time in error, for seven days during which time the edema increased to the previous degree. He was put on a salt free diet for a week without demonstrable effect. During the next three weeks no form of medication was given, he was kept on normal diet with

Middlesex County Sanatorium.
unrestricted fluids. Thereafter there was gradual decrease in the amount of edema and weight slowly decreased from 145 to 138 pounds but the N.P.N. increased to 50 mgms per cent and a week later to 55 mgms per cent. At this time he felt generally unwell. For the first time he complained of marked lassitude and there was a striking change in his mental well-being as he now had no interest in reading or in writing, saying that he felt too tired to do either, whereas previously and subsequently, these activities kept him continually occupied. When the N.P.N. was again occupied to catheterisation yielded 300 ccs. of clear sterile residual urine and he spontaneously gave the information that since shortly after starting isoniazid he could not empty his bladder properly, that it always felt partially full after urination and that there was diminished urinary stream. One week later the N.P.N. was 49 mgms per cent and the residual urine 170 ccs. In the following weeks there was an increased urinary output. The edema decreased though a trace remained around the ankles after exercise. Residual urine dropped to 75 ccs. and then to less than 10 and over this period the weekly N.P.N. readings were 46, 42, 42 mgms. per cent while the weight remained steady at 138 pounds. At this stage he volunteered that the vigour of the urinary stream was restored and the bladder felt empty after micturition. An intravenous pyelogram showed a normal pattern. Thereafter he continued symptom free until discharge in July 1954.

In this case the onset of edema and raised residual urine seemed to be related to isoniazid as they subsided when the drug was finally omitted and without other therapy. The fact that the N.P.N. continued to rise after stopping isoniazid has been noted by others and was also observed in the other cases.

Case 2: This was a 79 year old white male in whom pulmonary tuberculosis had been diagnosed by chest x-ray and bacteriological examination of the sputum at another hospital while under investigation for peptic ulcer. On admission the clinical condition was poor and he was much under weight. From the complaint he had minimal symptoms and examination of the lungs was within normal limits. There was slight prostatic enlargement, with a small nodule in the left lateral lobe which the consulting urologist did not consider malignant. Again on specific questioning the patient stated he had no symptom to suggest prostatic obstruction but had had no symptom to suggest prostatic obstruction. The urine was normal chemically and microscopically but of low specific gravity. An intravenous pyelogram done later was normal.

Treatment for radiologically proved gastric ulcer with bland diet, alkalies and Tr. belladonna m x v three times daily, was started simultaneously with streptomycin sulphate 1 gram daily and isoniazid 300 mgms daily (5 mgms per kilo of bodyweight). Within a week of starting treatment he developed acute urinary retention. At first intermittent catheterisation and later bladder drainage with a Foley catheter failed to produce relief and transurethral resection had to be done. At operation the bladder wall showed coarse trabeculation with numbers of cellules and small diverticulae. There was little if any hypertrophy. The prostatic urethra was extremely short and the urologist felt that the obstruction symptoms were due to a narrow sclerosis of the bladder neck. A minimal resection was carried out in all quadrants about 1 gram of tissue in all being removed. When this was done the bladder neck was wide open and there was no obstruction present. The pathological examination of resected tissue showed no malignancy.

After operation he made an uneventful recovery though obstinate constipation was troublesome. This latter complaint might have been partially due to impaction of barium in the bowel. He continued to take isoniazid in the previous dosage up to the time of discharge without further incident.

Case 3: In this patient complete retention, rising N.P.N. and mental confusion occurred in a young man after eight months of treatment with isoniazid but in whom the condition subsided when the drug was withdrawn, and without other specific treatment. This was a 38 year old white male who was admitted to the sanatorium on March 4, 1953 with far advanced pulmonary tuberculosis the diagnosis being made on x-ray film and bacteriological findings. He was known to have had diabetes since the age of 22 years and diabetic control had been poor because of his lack of attention to diet and insulin. On admission his general condition and nutrition were poor. Examination of the central nervous system showed a loss of knee jerks and diminution of vibration sense in lower limbs. The blood pressure was 120/80. Urine showed a heavy cloud of albumin, red and white cells and several fine granular casts. The N.P.N. was 44 mgms per cent. The prostate felt normal to rectal palpation. The consultant ophthalmologist reported no abnormality of eyes or fundi. Diabetic diet and insulin routine and treatment for tuberculosis commenced with streptomycin and para-amino salicylic acid. He proved to be sensitive to streptomycin and unable to tolerate PAS and consequently both drugs had to be stopped. On March 12, 1953 isoniazid 300 mgms daily (5 mgms per kilo of bodyweight) was commenced at which date the N.P.N. was 37 mgms per cent. On November 9, 1953 he developed complete urinary retention. The dosage of isoniazid was reduced to...
150 mgms daily and intermittent catheterisation was necessary. The blood N.P.N. was 65.5 mgms per cent. After a week during which he was restless, agitated and confused isoniazid was stopped and continuous Foley catheter drainage instituted. The N.P.N. had risen to 93 mgms per cent. In the following weeks there was slow improvement. On December 2, 1953 N.P.N. was 150 mgms per cent but he felt better. The Foley catheter was then finally removed and normal bladder function restored. Three weeks later N.P.N. had fallen to 48 mgms per cent and there was progressive symptomatic improvement. Bladder function continued normal up to the date of death six months later in uraemic coma with terminal hypertension. Permission for post-mortem could not be obtained.

Case 4: In this case the picture was less clear cut. He was a 77 year old white male who was admitted for treatment of far advanced pulmonary tuberculosis. He was a poor witness but it appeared that in the past he had had intermittent symptoms suggesting chronic prostatic obstruction with poor urinary stream and frequency with difficulty on initiation of micturition. For some time prior to the relevant date however he had no urinary symptom.

Treatment with streptomycin and PAS was commenced but a month later PAS had to be stopped as he was unable to tolerate it. Isoniazid 300 mgms daily was then commenced but all drugs were stopped one week later because of edema from ankles to mid thigh, and he had frequency and poor urinary stream though probably these symptoms were not markedly different from previous attacks. Weight had increased six pounds in five days. N.P.N. was 60 mgms per cent one week after stopping isoniazid. Edema subsided in a month without other therapy. No real conclusion as to cause and effect could be reached but it is possible that isoniazid did precipitate some mechanism leading to marked edema and recurrence of obstructive symptoms especially in view of the spontaneous remission after it was stopped.

Discussion

In case 1 an elderly but active patient developed edema and rising N.P.N. three months after starting streptomycin and isoniazid. There was a transitory improvement when the drugs were stopped but increased edema recurred when isoniazid was inadvertently given. The only evidence to suggest prostatic involvement was the high residual urine which in conjunction with the other abnormal findings subsided when the medication was finally stopped.

In case 2 the patient developed obstruction within a week of starting treatment. The drug was continued and transurethral resection was finally necessary; but after operation he was able to continue the drug without further trouble. The appearance of the bladder at cystoscopy suggested chronic obstruction though it had not caused symptoms. It is possible that the exhibition of isoniazid was sufficient to cause acute retention but when the obstruction had been cleared at operation he could tolerate the drug.

In case 3 the patient was young and a prostatic incident would not ordinarily be expected. He, however, had obvious renal damage with grossly abnormal urine. His would be the type of case in which a diabetic neurogenic bladder might occur. This however is usually irreversible and the relative rapidity with which the condition subsided when isoniazid was stopped suggests a causal connection. The possibility that the presence of impaired renal function can increase the side effects of isoniazid has been pointed out by Latimer.

In most series reported there has been some reference to urinary disturbance. Selikoff, Ornstein and Robitzev stated a number of cases receiving 1-10 mgms/kilo of Marsilid complained of dizziness, insomnia, constipation or urinary bladder retention and suggested an autonomic
origin either para sympathetic block or sympathetic stimulation. Robitzek et al when discussing iproniazid cite delay in micturition being one of the commoner side effects and more often seen in patients over the age of 50 years and comment on the fact that isoniazid has almost complete absence of toxicity. Benson, Stefko and Roe stated that tests to detect para sympathetic blocking action or atropine like activity could not be detected in animals. In the Medical Research Council report of the clinical trials reported in the British Medical Journal mention is made of three cases of disturbance of micturition in one of whom there was considerable delay is starting micturition. Dosage in that series was 200 mgms daily of isoniazid. Sweaney and Perez noted a rise in blood urea nitrogen in almost all cases treated, which usually levelled off in a few months without interrupting treatment, and, without causing ill effects.

It would be improper to attempt to draw conclusions from four cases but the strong impression has been gained that isoniazid does have a definite effect on bladder function. These cases taken in conjunction are suggestive that there may be a danger of precipitating a condition resembling prostatic obstruction which in young and relatively healthy patients may go unnoticed, but in those with impaired renal function, or in those in whom the balance between adequate bladder function and urinary retention is precarious the effect of the drug may be to add a moment which may imperil the patient.

SUMMARY

Four cases are reported in which isoniazid appeared to cause a prostatic obstruction syndrome. It is suggested that the danger of such a complication may be greater in elderly patients or those with poor renal function.

RESUMEN

Se relatan cuatro casos en los que la isoniacidad pareció causar un síndrome de obstrucción prostática. Se sugiere que el peligro de tal complicación puede ser mayor en los ancianos o en los que tienen deficiente función renal.

RESUME

L’auteur rapporte quatre observations selon lesquelles l’isoniazide semble avoir causé un syndrome de rétention d’origine prostatique. Il suppose que le danger d’une telle complication pourrait être plus sérieux chez des malades âgés ou chez ceux qui ont une fonction rénale défectueuse.

BIBLIOGRAPHIES