OBSERVATIONS ON THE USE OF
"BUTAZOLIDIN" IN ARTHRITIS

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The chance use of butazolidin (B.T.Z.) as a solvent of amidopyrine has led to claims of its potency as an effective analgesic, antipyretic drug. Belart (1949), Gsell and Mueller (1950), and others found the combined preparation to be of value in the rheumatic disorders and certain other conditions causing somatic pain. Wilhelmi (1949) investigated the action of various pyrazole derivatives singly, and concluded that B.T.Z. had particularly effective "anti-inflammatory" activity in animals. Pulver (1950) devised a method of estimating the level of B.T.Z. in the blood. Currie (1952) has reported favourably on the effect of this drug.

We were not prepared to use amidopyrine, but decided to undertake an investigation into the use of B.T.Z. alone. One hundred cases have been given this preparation during the past six months, and a broad field was covered. This has included estimation of dosage schedules, oral dosage, and the effects in a variety of clinical conditions. For controlled investigations rheumatoid arthritis was selected, and the cases chosen were treated on an out-patient basis. More complete studies were made on a smaller number of in-patients.

Methods

The assessment of rheumatoid arthritis is notoriously difficult. Out-patients were chosen for controlled investigation primarily because functional improvement can best be measured by the patient in performing everyday activities under familiar conditions. All out-patients in this series had been under observation for many months and in some cases for years. Progressive cases of typical rheumatoid arthritis with persistent pain which had not improved on the usual treatment (physiotherapy, rest, and gold) were accepted for trial. Those presenting severe constitutional symptoms were dealt with separately as in-patients. In order to eliminate, so far as possible, the factor of suggestibility in both patient and doctor, two sets of identical ampoules were prepared—one containing the substance under review, an almost colourless watery solution, and the other saline. These were issued by a pharmacist, who alone knew the nature of the contents. The only information given to him was the sex and age of the patient and the severity of the disease. Two approximately comparable series were thus obtained. A standard form of assessment was prepared, and all patients were examined before and after four weeks of treatment. In many cases intermediate examinations were carried out.

The experimental course of treatment consisted of 1 g. of B.T.Z. by intramuscular injection daily for ten days, then every second day for ten days, and every third day for three further injections. The outer aspect of the thigh and the upper, outer quadrant of the gluteal regions were

the sites of injection. At the outset it was thought that this preparation might prove most useful in the rheumatoid group of diseases. A number of cases suffering from osteoarthritis of the hip were given the same course of treatment in the expectation that they might serve as a second controlled series, against the possibility that this substance acts as a "superior form of aspirin." In fact, this group showed striking symptomatic improvement.

All patients, treated and controls alike, were told that they were to be given a new and unproved drug unrelated to cortisone. It was refused in only one instance. A different procedure was followed in those admitted to hospital. B.T.Z. was given only if no improvement had occurred after at least three weeks' rest with physiotherapy and adequate salicylate therapy. Alternating courses of B.T.Z. and the control solution were given, the nursing staff and patients being unaware of the various changes.

Results

An analysis of material is given in Table I and the clinical assessment of the results is shown in Table II.

TABLE I.—Analysis of Material

	Control Cases	B.T.Z. Cases
Males	6	5
Females	10	11
Average age	49.6 years	51.9 years
Average duration	7.75 "	9.1 "
Clinical assessment:		
Mild	6	6
Moderate	9	7
Severe	1	3

TABLE II.—Clinical Assessment of Results

	Worse	Unchanged	Improved	Excellent
Control cases	3	11	2	0
B.T.Z. cases	0	2	9	5

Joint Tenderness (Table III).—The technique of Quin, Mason, and Knowelden (1950) was used. Four degrees of tenderness were recognized: grade 1, no tenderness; grade 2, subjective tenderness; grade 3, the patient winced in addition to expressing discomfort; and grade 4, wince and withdrawal. The most tender joint, often a proximal interphalangeal joint, was chosen for testing, but the response at one or more other joints was usually noted to allow for the normal slight variations in joint tenderness.

TABLE III.—Improvement in Joint Tenderness

	Control Cases	B.T.Z. Cases
Initially Grade 4:		
Improved 3 grades	0	3
" 2 "	1	3
" 1 grade	1	3
Unchanged	6	0
Initially Grade 3:		
Improved 2 grades	0	2
" 1 grade	1	3
Unchanged	7	2

Grip.—This was assessed by the sphygmomanometer-cuff technique (Quin *et al.*, 1950). The results are expressed as the average grip, in mm. of Hg, of three readings in each hand, measured before and after treatment (Table IV).

Timed Activity.—One or two habitual activities unlikely to be influenced by the conditions of examination or improved by practice—for example, a standard walk, putting

TABLE IV.—Assessment of Grip

	Control Cases	B.T.Z. Cases
Before treatment	143 mm. Hg	140 mm. Hg
At end of treatment	140 " "	183 " "

on and tying laced shoes, etc.—were selected for each patient. These involved the use of one or more of the affected joints. These actions were timed before and at the end of treatment (Table V). The two groups are not directly comparable in this test, since the walking distance varied in different hospitals. Nevertheless, the proportional improvement in the B.T.Z. group is obvious.

TABLE V.—*Timed Activity*

	Control Cases	B.T.Z. Cases
Average times before treatment..	56 seconds	94 seconds
" " after " "	55 "	61 "

Osteoarthritis of the Hip

The average age of the 16 cases in this group was 69.1 years, and both hips were affected in five cases. The average duration of symptoms was 2.7 years. In all cases no significant relief had been obtained from one or more other types of treatment. These included deep x rays, procaine-lactic-acid injections, short-wave diathermy, and non-weight-bearing exercises in the "slings and springs." The first five cases had the same dosage schedule as for rheumatoid arthritis. The analgesic effect was dramatic, and, since on this evidence B.T.Z. was a potent analgesic with a blood level maintained for at least 48 hours, it was decided to give the remaining cases 1 g. intramuscularly every second day for the first ten days and every third day thereafter. This scheme did not seem to reduce the analgesic effect. Three of these patients became virtually pain-free. Eight experienced a great deal of relief—that is to say, they had no night pain and only a small amount of aching when standing or walking. Two patients did not appear to derive quite as much benefit, and in a further two the degree of relief was slight. In all but one case nocturnal pain was virtually abolished, with resulting improvement in sleeping.

Further Observations

Amongst in-patients under treatment a striking effect on pyrexia was seen. This is shown on the temperature chart of one severely ill case of rheumatoid arthritis which had resisted all forms of treatment for thirteen weeks (see Chart). In parallel with a dramatic clinical improvement the temperature fell within 24 hours of the first injection. Clinical improvement and normal temperature continued under the influence of B.T.Z. and both relapsed when it was withdrawn.

Our observations support the pharmacological findings of Pulver (1950) in animals and of Gsell *et al.* (1950) in human subjects. These observers noted that the preparation attains high concentrations in the blood soon after injection and

falls over 48 hours to a low level that persists for at least a further 48 hours before finally disappearing. As may be seen in the Chart, the antipyretic effect lasted for 48 hours after withdrawal. The same observers failed to demonstrate any cumulative effect. This accords with our experience. In addition we did not find any increased clinical effect with larger doses up to 2 g. daily. Some cases were treated orally, with a comparable response by clinical assessment.

The possibility of a cortisone-like action is unlikely, since no change in ketosteroid levels, haemoglobin concentration, eosinophil counts, or blood pressure was found. In one patient with coincident diabetes the carbohydrate metabolism was unaffected. In contrast to the findings of Currie (1952), no effect on the erythrocyte sedimentation rate was observed.

Toxicity

A frequent check of the white-cell count was carried out on all cases. No evidence of any adverse effect on the granulocyte series was found. The maximum period under observation and treatment so far is nine months.

Intramuscular injection of B.T.Z. in solution is usually painful, the pain lasting up to half an hour. Two inflammatory reactions at the site of injection subsided without incision; these were probably due to faulty technique.

Mild gastro-intestinal disturbance and nausea rather than looseness of the bowels have occurred in about one-quarter of our patients. In two the nausea was severe enough to indicate withdrawal. One case developed diarrhoea, which did not reappear on resuming the drug at a lower dosage after temporary withdrawal. Commonly, the disturbances have been transitory even though treatment was continued.

Water retention has been observed in eight patients who developed oedema of the legs. Treatment was stopped on this account in two cases. The oedema disappeared when dosage was reduced and salt intake restricted in a further five cases. In one in-patient who developed considerable oedema the electrocardiogram and the electrolyte and serum protein levels were all normal, and the oedema disappeared within a week although treatment was continued. Salt restriction was the only therapeutic measure taken.

Three patients developed drug rashes. Two of these were transitory and did not reappear on resuming B.T.Z. In a third the rash was accompanied by nausea, pyrexia, and malaise. No change in blood chemistry was detected and the condition remitted five days after withdrawal of the drug. One patient developed a pyrexial illness characterized by dyspnoea without abnormal physical findings. The full blood count and a chest x-ray film did not show any abnormality. The condition subsided in a week. B.T.Z. was not given to this patient again.

Chart showing antipyretic effect of butazolidin.

One patient developed extensive purpura after a fortnight. This resolved within a week on stopping B.T.Z. No change could be demonstrated in blood count, platelet count, or bleeding and coagulation times. One month later, at half dosage, the purpura reappeared, but was much less pronounced, after 1 g. had been given by mouth. Again no blood changes were found.

One death has occurred in the course of this investigation. Neither the clinical course nor the full post-mortem examination, including neural histology, gave evidence of the nature of the morbid process. The case history is given below.

A West African negro aged 26, who had been resident in this country for three years, was admitted to hospital with less than a week's history of pyrexial illness with joint swelling. A similar episode, 18 months previously, had been investigated elsewhere with negative results. He was febrile and had a painful polyarthritis involving some large joints and the interphalangeal joints of the hands. Examination was otherwise negative. The following investigations yielded normal results: blood count, blood cultures, Widal, brucella agglutinations, films for trypanosomes and malaria parasites. The urine and cultures of throat swab, urethra, and stools yielded no pathogens, and the E.S.R. was normal. The Wassermann reaction was negative, but both the Kahn test and G.C.F.T. were weakly positive. His condition did not change in three weeks despite courses of salicylates in large doses, penicillin, and quinine. He was then given 1 g. of B.T.Z. intramuscularly daily for nine days. Pyrexia and pain remitted within 12 hours of the first injection. On the eighth day fever returned and tender occipital glands were found. Full blood investigations were normal. The drug was discontinued the next day, but his condition was unchanged and he died four days later, quite suddenly, after two convulsions.

This patient's illness and death remained unexplained. It is noteworthy that B.T.Z. was discontinued four days before the fatal termination. Although we had no positive evidence to incriminate the drug, equally a toxic reaction cannot be excluded.

Discussion

We have now given B.T.Z. in more than 70 cases of rheumatoid arthritis. It has produced improvement which has been impressive and at times dramatic. In only two cases did it appear to be ineffective. The results of the controlled experiment are expressed in Tables I-V and are superior to those obtained with any form of therapy at our disposal, in particular in the relief of pain. It has proved remarkably effective in relieving the pain of osteoarthritis.

These results do not suggest that B.T.Z. is in any way curative. Continuation treatment has been necessary and return of symptoms has occurred at a variable period after withdrawal of the drug. This interval is usually three to seven days, but in one case was six weeks. No alteration in the sedimentation rate or haemoglobin level has been observed, and in those patients whose muscles showed wasting no increase in muscle bulk occurred. A longer period of observation is required to reach conclusions upon the effect of increased mobility of the patient on joints controlled by weak muscles. Our patients have been advised not to exceed their usual "walking distance" despite the degree of relief from pain which most have experienced.

Although we have recorded the reactions and possible toxic results in detail, it must be stressed that these are drawn from all patients to whom we have given B.T.Z. up to the time of writing—that is, 100 cases. These have included examples of conditions other than those discussed in this paper.

Summary

Observations on the use and toxicity of butazolidin are presented.

Butazolidin has produced remarkable symptomatic relief in a high proportion of cases of rheumatoid arthritis. It is believed to be analgesic and antipyretic rather than curative in its effects.

The degree of relief experienced by cases of osteoarthritis was impressive.

APPENDIX

Further observations, on a total series of cases now exceeding 200, have been made. We have extended our therapeutic trials and are satisfied that butazolidin is of value in a wide range of painful states. These are confined to skeletal conditions.

Relief from pain and increased functional activity have been obtained in ankylosing spondylitis, degenerative joint disease of the spine, and painful Paget's disease of bone. In psoriatic arthritis we have found the joint lesions to be relieved but the skin lesions to be unchanged. In rheumatic fever the drug is at least as effective as salicylate therapy.

For our most recent out-patient cases we now use only oral treatment. One gramme daily, in divided doses, is given for at least three days, and then 1 g. on alternate days for two to four weeks. The dose is then progressively reduced until the lowest effective level is found—usually three or four 200 mg. tablets on alternate days, or even twice a week.

Fluid retention is so common a side-effect, though often transient, that we tend to avoid the use of butazolidin in the older subjects and in those with diminished cardiac reserve. We do not give the drug to patients with a definite history of peptic ulceration and are cautious with those who have marked dyspeptic symptoms.

We are indebted to those physicians of the West Herts Group who have made additional beds available for this experiment, and to Mr. C. Dawson, lately chief pharmacist at the West Herts Hospital, for his assistance. To the Pharmaceutical Laboratories, Geigy Ltd., we are indebted for generous supplies of butazolidin.

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A CASE OF PULMONARY MONILIASIS

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A few cases of pulmonary moniliasis have been reported from time to time. As the disease has no constant symptomatology, the diagnosis is often difficult and a good proportion of cases escape detection. One difficulty in diagnosis is due to the resemblance of the disease to pulmonary abscess and tuberculosis; but moniliasis should be kept in mind and careful examination of the sputum made.

The patient whose case history we record here had a large cavity in the right lung; but as the symptoms and signs were not typical of abscess of the lung and the tubercle bacillus was absent from the sputum on repeated examinations, we were prompted to search for other agents and were thus able to diagnose moniliasis.

Case History

A man aged 58 was admitted to hospital on December 4, 1950. His past history was not relevant. Four months before admission he began to complain of fever and fatigue.