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Use of tolserol as a diagnostic and prognostic aid in low back disorders

Theodore John Lemke Jr
University of Nebraska Medical Center

THE USE OF TOLSEROL AS A DIAGNOSTIC AND PROGNOSTIC AID IN LOW BACK DISORDERS

Theodore John Lemke, Jr.

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INTRODUCTION

The purpose of this paper is an attempt to evaluate, from past and current literature, the role of Tolserol, a specific type of muscle relaxant, as a diagnostic and prognostic aid in the acute low-back syndrome. The pathological entities responsible for the low-back syndrome are multiple and include among them; injuries to the intervertbral disc, actual trauma to the supporting structures, changes in the supporting structures, as from rheumatic disorders and apophyseal joint disease. Many other etiological factors must certainly exist, and because they exist, the underlying mechanisms in acute low-back disorders, with or without radicular pain, are not always clear. In the majority of rheumatic disorders, spasm of muscles is responsible for a considerable degree of the disability, discomfort and loss of function. It may be produced by exposure to excessive heat or cold, overextension of the muscle, sprains, strains, direct injury, overindulgence in unaccustomed activity, and atrophy of muscle. Schlesinger (1) states that it is fortunate that whatever the basic stimulus initiating the acute low-back picture, the reaction pattern is fairly constant. Any local insult to the vertebrae and supporting structures provokes the characteristic response of splinting to pre-

vent further trauma or pain. This characteristic splinting or spasm may have an acute, subacute or a gradual onset, manifested by any degree of disability from mild stiffness to severe limitation of motion of the joint. Spasm of the muscle is often of short duration, disappearing spontaneously if it can be dissociated from pain. However, the realization that immobilization relieves pain may initiate what might be termed "habit spasm" within a matter of hours or days. The transition from ordinary spasm to "habit spasm" ordinarily occurs without the knowledge of the patient. The original disability may then be continued indefinitely, and the condition may change from an acute one to a chronic disability characterized by the "habit spasm", voluntary limitation of motion, and disability, all associated with pain. Smith (2) states that physiatrists are aware of the part spasm of muscle plays in many acute musculoskeletal disorders, so that often more attention may be given to the secondary spasm of muscle than to the original cause of the acute disability.

Schlesinger and Ragan (3) have shown that the various lesions which together make up the low-back syndrome are excellent examples of the importance of the problem of muscle spasm in treatment.

The goal of therapy in neuromuscular disorders lies in increased efficiency of performance and relief of discomfort. Except specific surgery and drugs which have muscle relaxant qualities, traditional physical therapy has the most to offer. Strengthening and co-ordination excercises, the improvement of habit patterns and the employment of prostheses often contribute a great deal. Frequently, however, there are present neuromuscular abnormalities which either make positive therapy difficult or are actually potentiated by active motion. In such cases an attempt to ameliorate the abnormal bombardment is critically important.

Muscle spasm is a reflex defense phenomenon, characterized by a prolonged contraction not amenable to voluntary control, resistance to stretch and by diffuse, severe, poorly localized pain (4).

Normally, muscle stretch elicits afferent impulses arising in the muscular spindles. These impulses are conducted back to the cord, and a reflex contraction is then initiated by way of the motor side of the reflex arc. This is the basic stretch reflex of Sherrington. When there is a pathologic change somewhere in the system, there may be a potentiation of this cycle (4). The threshold of the arc is lowered, and the response becomes more active than in normal circumstances.

Thus we have the mechanism for a self-perpetuating circuit, the vicious cycle of pain and splinting or spasm. Attempted movement elicits pain and further splinting, then more pain, and so on. Schlesinger (1) has shown that at times, the vicious cycle of pain and muscle spasm may so aggravate the symptom complex that it is difficult to consider the muscle spasm as purposeful and may occasionally resolve itself with the simple relief from the muscle spasm. The effects of relief from muscle spasm alone make one wonder if it plays a part other than that of secondary protective splinting in the syndrome complex. Several possibilities are conceivable. The splinting may perpetuate the symptoms by fixing the involved parts in an abnormal position, by encroaching upon the blood supply to the area, or by increasing venous congestion. Splinting may also prevent reduction of the root compression by maintaining the vertebral elements in a particular position. This is the condition that may lead to chronicity, unless measures of relief are instituted.

The traditional methods of achieving muscle relaxation mentioned before (4) are well known and fairly efficient at times. Unfortunately they are not specific and often are quite time-consuming. Since any safe means of obtaining a rapid dissolution of skeletal muscle spasm is of special interest to the orthopedic

and to the neurological surgeon, techniques are legion and represent widely varying approaches. Within recent years the group of pharmacological agents which afford specific muscle relaxation has undergone a great amount of study. Of the group, the drugs with the most useful qualities clinically are the quaternary ammonium salts, exemplified by curare, and the substituted ethers of glycerol, such as Tolserol.

HISTORY

The manner in which this series of drugs, the substituted ethers of glycerol, came under investigation is of interest. In England, in 1946, phenoxetol was being used as a preservative for penicillin. Berger (5) was asked to study the pharmacologic side effects of this drug and he found that this drug had muscle-relaxant qualities, but of a low order. Berger and Bradley (5) began a systematic investigation of the pharmacological properties of alpha-substituted ethers of glycerol and found that certain of these compounds produced paralysis with profound muscular relaxation. Their experimental work was done on mice, rats, and guinea pigs. They found that small quantities of these substances produced tranquillization, muscular relaxation, and a sleep-like condition from which the animals could not be aroused. Larger doses produced ataxia,

which was followed by paralysis. The animals did not react to painful stimuli and were unable to turn over when placed on their backs. Paralysis was followed by complete recovery. In all, 143 of the compounds were examined and of all tested the substance, which was subsequently named "myanesin", proved to be the most potent and safest and had the widest margin between the paralysing and lethal doses.

This led to prompt clinical trials of the drug as an adjunct to anesthesia by Mallinson (6), who reported almost complete abdominal relaxation in low dosages, with no intercostal paralysis in doses producing full relaxation of the abdominal muscles. Soon, however, reports were being made of the side effects of myanesin which included a localized thrombophlebitis at the site of injection of the drug (7), and of a transient, but often serious, hemoglobinuria (8). Schlesinger, Drew and Wood (9) accounted for these side effects on the basis that previous to their experimentation with the drug it had been used as a 10% myanesin in propylene glycol and alcohol solution and in addition, the adjuvants necessary to maintain solution at the 10% concentration obviously interfered with a study of pure drug effects. Their experimentation was performed with a 2% solution of myanesin in normal saline which proved

to be stable and yet clinically effective. The bulk necessary for administration of the 2% solution of myanesin was considered of only minor importance. The success achieved with the 2% solution aroused new interest in the drugs use since the side effects previously reported with the use of the 10% solution could now be considered overcome.

PHARMACOLOGY

The pharmacological properties of Tolserol, the trademark of E. R. Squibb and Sons for myanesin, have been thoroughly investigated by numerous individuals. Berger and Bradley (5) were among the earliest of the investigators. Their first opinions were that the drug produced paralysis by either a block at the myoneural junction (curare-like action) or to direct action on the nerve (local anesthetic action). Later in their first experimental work they found that myanesin had marked anti-convulsive properties when strychnine was give to produce the convulsions. This suggested to them that myanesin exerted a depressant action on the reflex excitability of the spinal cord. This was not in accord with the theory that myanesin produced its effects through a curare-like action because when curare was administered in a similar way, it produced

an additional stimulation of the cord or an aggravation of the effects of strychnine. No central action was attributed to myanesin by Berger and Bradley (5) because it did not effect conciousness and never caused prenarcotic excitation. Only in the case of lethal dosage did they find the muscles of the diaphragm paralyzed (10).

Richardson, Morrison and Walker (11) reported that myanesin appeared to be a very short-acting basal anesthetic. This was upheld by Schlesinger (12) in his early work, although he could not account for this quality of the drug. Stephen and Chandy (7) were the first investigators to refute this and went on to report that this was one of the unique features of the drug, namely, that myanesin could produce muscular relaxation and yet not impair strength or conciousness. They produced evidence in the form of electroencephalogram patterns which demonstrated that there was no effect upon cerebral structures by the drug. From their observations they concluded that the chief site of action was upon structures lying between the cortex and the spinal cord. Berger (13) ruled out the possibility of the direct action on voluntary muscle or on the peripheral nerve. This was supported by Griffith, Rand and Cullen (14), who in addition stated that

the drug had no measurable effect on synaptic transmission of impulses through the spinal cord. This was later confirmed by Griffith, Stephen, Cullen and Bourne (15) after a series of 220 cases observed clinically. One can observe from the above and what is to follow how the scientific mind must eliminate, in order of possibility, those factors enroute to the ultimate goal.

Gammon and Churchill (16), reporting from clinical observations, were the first to recognize a central effect of myanesin by, what they described as a differential action upon the basal ganglia, brain stem and perhaps thalmus. Henneman, Kaplan and Unna (17) reported reduction of facilitation and inhibition of the knee jerk resulting from cerebral cortical stimulation. This, they reported, was a direct action upon the bulbar reticular formation. This was again confirmed by Unna and Kaplan (18).

It was now becoming apparant that myanesin was a drug which had the ability to depress the central nervous system with a high degree of specificity. This was in contrast to previously known drugs, such as curare, which exerted a more generalized effect.

Henneman, Kaplan and Unna (19) reported by far the most extensive experimental coverage of a study of the effects of Tolserol on motor systems.

They began their investigations on the effect of myanesin on facilitation and inhibition originating in the bulbar reticular substance. Here, in the lateral reticular nuclei, all forms of somatic motor activity, reflex as well as voluntary, facilitation takes place. In the medial reticular nuclei, stimulation will produce an inhibition of all reflex or voluntary activity. These two nuclear aggregates give rise to reticulospinal tracts which descend in the lateral and ventral funiculi of the cord. They convey facilitatory and inhibitory impulses by appropriate propriospinal relays and by a few direct connection to anterior horn cells at all levels of the spinal cord. In their experiments they proved, with the aid of an electromyogram, that facilitation could be completely depressed with lower than therapeutic dosages. Inhibition, on the contrary, could not be abolished with three to four times this amount.

Next they studied the effect of Tolserol on its effect to abolish facilitation and inhibition from higher centers, namely the motor cortex, caudate nucleus, and cerebral cortex. In each of these systems it was found that Tolserol completely abolished both facilitation and inhibition, but in greatly reduced dosages. Finally, they studied the effect of Tolserol on fac-

ilitation and inhibition at a spinal level. For this experiment the spinal cord was sectioned at a high thoracic or cervical level so that the neural circuit to be studied was entirely spinal and devoid of central effect. This proved to be their most valuable contribution for it was here that they found in stimulating a monosynaptic circuit, inhibition could be eliminated only short of eliminating the animal with such large, lethal doses of Tolserol.

From their work they concluded that Tolserol decreases or abolishes facilitation and inhibition reaching anterior horn cells from all levels of the central nervous system. It accomplishes this by an action upon internuncial cells, for the direct circuits withstand large doses without effect. Facilitatory and inhibitory systems exhibit resistance to the drug in proportion to the percentage of direct or internuncial elements they contain.

The segmental levels at which Tolserol acted was explained on the basis that the longer and the more complex the circuit, the more vunerable it was. Thus, the internuncial neuron was established as the site of action of Tolserol.

Further investigation by Henneman and Scherrer (20) on the effect of Tolserol in spasticity substantiated

the earlier claims. Miller (21), reporting from clinical observations, stated that Tolserol affects muscle groups in different order and to varying degrees. He maintained that the muscles on the posterior half of the body are first affected, then the action reaches the peripheral and intercostal muscles, subsequently the cranial muscles, and last the diaphragm. Hovda (22) later reported that when Tolserol was given in dosages which abolished the myotatic reflex arc, facilitation could no longer be elicited.

Stephen and Chandy (7) made an additional clinical observation of the reduction or abolition of pain of central or thalamic origin. Schlesinger, Drew and Wood (9) described the pain relief as being local in nature and stated it to be procaine-like in effect. Kaada (23), however, reported that the local anesthetic effect of Tolserol was not sufficient to account for the relief he had observed in intractable pain of central origin. He proposed that the pain-relieving effect of the drug might be attributed to a depression of hyperactivity in subcortical integrative pain centers, in which complex multineuron pathways are involved.

ADMINISTRATION

One of the early limitations of the use of Tolserol

was the route of administration. It was first used (5) as a 10% solution of myanesin in propylene glycol and alcohol. This solution produced the toxic effects described previously (7,8,9). Subsequently (9), a 2% solution in normal saline was prepared which did not produce the toxic effects. Both of these solutions were administered intravenously. Oral administration was attempted by Schlesinger, Drew and Wood (9), who reported that this yielded completely unpredictable results with inefficient therapeutic effects at best. They also reported that the oral administration seemed to cause a greater incidence of nausea than any route of administration. Intramuscular injection of myanesin in concentrations higher than 2% was found to lead to necrosis and evidence of severe inflammatory reaction in the tissues. These changes were not seen when a 2% solution was used, but the bulk necessary for effective doses of the 2% solution by the intramuscular route made such a technique of administration unfeasible.

Berger and Schwartz (24) were the first investigators to report favorably of the use of Tolserol by the oral route. This was in the form of an elixir with 3.3% (weight in volume) solution of Tolserol in 20% (volume in volume) aqueous propylene glycol, with syrup of cherry 20% (volume in volume) to improve the taste

of the mixture. They reported excellent results with only rare incidents of side effects demonstrated. They encountered no nausea or vomiting, hemoglobenuria, and only several patients experienced a transient feeling of lassitude for ten to twenty minutes after administration of the drug which did not, however, prevent them from carrying out their usual duties. Subsequent reports (2,16,25,26,27) have acclaimed the oral route as being highly effective. Hermann and Smith (28) administered oral Tolserol to a series of 200 patients and found the oral capsules to be slightly superior to the oral tablets or the elixir. Another limiting factor in the intravenous administration of Tolserol was the evanescence of clinical effect (22,29,30). Supporters of the oral route of administration report that this has been overcome.

AS A DIAGNOSTIC AND PROGNOSTIC AID

The frequency with which affections of the low back are encountered brings them constantly to the attention of every practitioner of medicine. Patients whose low back pain is caused by visceral rather than musculoskeletal lesions or is an hysterical conversion symptom associated with tension, nervousness, and chronic fatigue will not be discussed here as they are entirely

different problems of diagnosis. The variety of bone and joint lesions which may cause low back pain and the difficulties encountered in their treatment make these affections formidable orthopedic problems. In each case the diagnosis and treatment must be based upon a careful evaluation of the clinical and roentgenographic findings in the light of available information on the various recognized types of low back lesions. As is often the case, however, roentgenographic findings are of little help toward making a positive diagnosis and are then used to rule out the various entities which would show positive roentgenographic findings. Diagnosis must then be based upon an evaluation of the clinical findings. It is here that it is felt that Tolserol can be a valuable aid. Once the diagnosis has been positively established, treatment can be instituted.

Treatment of the disorders which make up the acute low-back syndrome must obviously be of two types. Specific treatment, when available, is generally of the radical or operative type and its application is contingent upon the results of conservative or non-specific therapy. Non-specific therapy consists in the use of agents for the relief of pain and in attempts at gaining enforced rest for the affected parts.

The choice between operative treatment and protracted conservative treatment is often difficult. Schlesinger and Stinchfield (1) stated that is was often most discouraging to confine a patient to bed for long periods of time and then subsequently be forced to abandon such treatment for operation. To many patients the gamble on conservative treatment is economically unfeasible, and they may be forced to demand operative relief for other than sound medical reasons. They (1) felt that if one has reliable information upon which to predict a good result with conservative treatment, it is much easier to be convincing about traction, protracted bed rest, physical therapy, and braces. They then set out to see if such reliable information could be gained with the use of Tolserol. For their work they chose only those patients who were admitted to the hospital with the diagnosis, physical signs, and severe complaints of intervertebral disc disease. Each patient, shortly after admission, was given an intravenous injection of approximately 100 cubic centimeters of 2 per cent solution of Tolserol. A careful record of the patient's ability at straight-leg raising was made before the injection was given, together with the data from the usual neurological and orthopedic examinations. As soon as the therap-

eutic level, which is evidenced by the appearance of a vertical nystagmus, was reached, after injection was started, the patient's ability at straight-leg raising was again tested, both for actual range and for the point at which pain could be easily elicited. They then continued the injection until the total of 100 cubic centimeters was given with repeated testing of the range of straight-leg raising. No forced elevation or manipulation was carried out. Their report is based upon a series of 64 such cases. The results are extremely interesting. In compiling the data received, they found that the reactions to the injection of the 100 cubic centimeters could be grouped into the following categories:

1. In the first group, there was an abrupt relief from pain and a concomitant striking increase in range of motion, both of which were maintained for varying periods.

2. In the second group, there was also an abrupt relief from pain and a moderate or small increase in the range of motion, both of which were again for varying periods of time, but usually for a shorter duration than the first group.

3. In the third group, there was an abrupt relief from pain with no increase in the range of straight-leg raising. In this group, however, there was

an equally abrupt return of pain on the cessation of injection.

4. In the fourth group, there was rapid relief of back pain and "tightness", but with an increase in radicular pain. Interestingly enough, these patients often volunteered with the comment that they had then to hold their backs stiff to prevent pain. The relief from pain was of short duration, and their ability in straight-leg raising was never increased, and on occasion, even decreased.

The primary effect of Tolserol, as previously stated, is specific potent muscle relaxation, while the secondary effect is analgesic. Consequently, the therapeutic results listed above must be considered as the direct results of the reduction of muscle spasm and transient analgesia. The fact that pain did not abate in certain cases is fair evidence that the analgesic effect is not the major factor in the varying clinical results or responses.

Schlesinger and Stinchfield (1) gave the following interpretation for the four types of results:

1. The patients who showed immediate relief of pain and increased motion, with maintenance of effect over relatively long periods, were considered to represent examples of reversible root compression. The

dramatic response obtained may have been due to the effect of reversible root compression or due to the effect of relieving muscle spasm and its sequelae on the local pathological mechanism.

2. Those patients who responded obviously to motor relaxation, but not so dramatically as those in the first group, were considered to represent a variation of the first group. Muscle relaxation might have for them a definite therapeutic effect upon the etiological factors responsible for the syndrome, but of lesser importance. Conversely, muscle spasm might have a part in perpetuating the syndrome, but not in so great a degree.

3. Those patients who had an abrupt relief from pain and rapid return of pain on the cessation of the injection, but who had no increase in mobility, were felt to represent cases in which root compression was direct, mechanical in type, and not amenable to the effects of muscle relaxation. In other words the part played by muscle contraction in maintaining root compression was minimal.

4. Those patients who had relief from back pain with increased radicular pain and diminished straight-leg raising indicated marked root compression. In these cases the reduction of muscle splinting of purposeful type increased the degree of root compression

of a mechanical, direct nature. Straight-leg raising was decreased, and voluntary splinting was often necessary to relieve root pain. These apparently represent cases of truly purposeful muscle splinting, with severe root compression slightly alleviated by the splinting and made worse by its dissolution.

Subsequent follow-up studies on these patients confirmed the validity of the above interpretations. Of the first group, containing 25 cases, all of the patients left the hospital symptomatically well after a period of conservative treatment. One patient of this group had a return of symptoms one year after the initial hospitalization and was later operated upon. Of the second group, consisting of 13 cases, five patients were brought to operation after a brief period of conservative treatment, to which they were not responding satisfactorily.

All of the patients in groups three and four, totaling 26 cases, came to operation shortly. In every instance the operative report was of inexorable root compression by large herniations of the nucleus pulposa or protrusions of the intervertebral disc. Only group two was not subject to a clear-cut interpretation or correlation with regard to the end result. It is apparent that, with this type of response, the

test lacked real prognostic significance. The mode of treatment in those cases was a direct outcome of the long-term response to conservative or traditional management. However, it can be seen that the savings in both time and money to the patients in the other three groups would be considerable, not to mention sudden relief of severe pain and suffering which most certainly would have existed under traditional methods of management.

All of the above work by Schlesinger and Stinchfield was done using a 2% solution of Tolserol in normal saline (1). They stated that although it was purported to be effective by mouth, it was not so in their experience and, at any rate, the levels necessary to obtain rapid relaxation could not be attained easily by oral administration. They (1) went on to report that the drug has an analgesic effect similar to that of aspirin, and, in large part, this fact was responsible for its reputed effect when taken by mouth.

Berger and Schwartz (24) maintained that they could obtain adequate relief of both muscle spasm and pain by using the oral route.

Schlesinger (12) stated that it is often of prime importance to both the orthopedist and neurologist to determine if seeming deformities and contractures,

as often seen in hyperactive stretch response, are reversible and thus amenable to physical therapy or if they are static and require more radical therapy. In the arthritides of the spine, Schlesinger (12) saw new diagnostic abilities of Tolserol. After the relief of pain and muscle spasm, which are both of severe degree at times, there is found a restoration of mobility. It can then be determined if ankylosis will ever permit return of function, and if so proper physical therapy measures can then be instituted.

Lumbosacral or sacroiliac strain comprise the most common of the orthopedic causes of low back pain with an acute onset, usually traumatic. Of the two, lumbosacral strain is the more common. This is because the lumbosacral joint, situated at the critical level between movable and immovable portions of the spine, is particularly liable to injury from forces applied in an obliquely anteroposterior direction, as in violent flexion or hyperextension of the spine, falls upon the buttocks, and gravitational stresses associated with excessive lordosis. Smith (2) reported favorable response with the use of Tolserol to relieve the muscle spasm here. It is to be noted, however, that it was used in conjunction with traction and other traditional forms of conservative therapy.

Hermann and Smith (28) reported significant results from the use of Tolserol in two hundred cases in the treatment of rheumatic diseases. Included in this group were patients with rheumatoid spondylitis, lumbosacral sprain and strain, lumbago, and fibrositis. All were treated with oral preparations of Tolserol. They reported that all of the patients in the group with rheumatoid spondylitis had excellent results and were so improved that no additional medication was required for discomfort, and motion was greatly increased. Sixteen of the eighteen patients in the lumbago group had good relief from pain and muscle spasm. Several patients in this group had recurrent attacks and all responded favorably to a three day course of oral Tolserol. There was no recurrence of symptoms when it was discontinued. In the groups with lumbosacral sprain and strain and fibrositis, symptomatic relief was obtained in a large majority of the patients. It must be remembered that in these instances, the symptomatic relief of pain and muscle spasm is the chief objective of the users of Tolserol. The pathology present in the lesions is only indirectly affected by the use of the drug, as when motion or mobility is restored.

SUMMARY

Tolserol is a specific muscle relaxant drug of the substituted ethers of glycerol series. It was first thought to exert its effects by a curare-like action, but this was later proven erroneous. Instead of a peripheral effect, it decreases or abolishes facilitation and inhibition reaching the anterior horn cells from all levels of the central nervous system. It accomplishes this by depressant action upon the internuncial neurons, spinal as well as central. Direct, or monosynaptic, circuits withstand large doses without effect. The medial and lateral reticular nuclei of bulbar substance appear to be the chief sites of action.

Tolserol has proven itself to be of value in the establishment of a more positive diagnosis in the "acute disc syndrome". After the administration of the drug, the patient is checked for relief of pain, increase or decrease in range of motion, and when present, the return of symptoms, muscle spasm and pain. In those patients who exhibited relief of pain but with a decrease in range of motion compared to the range of motion they had previous to the administration of the drug, it was found, substantiated by operative report, that this represented root compression

of a direct and mechanical nature by an irreducible nucleus pulposa. If, however, the pain and muscle spasm were abolished with maintenance of effect over relatively long periods, it was felt that this then represented examples of reversible root compression. Patients exhibiting variations between these two extremes were followed closely by the conservative or traditional method, but the saving of time and money of the patients was great.

Tolserol may be given orally or intravenously, but some investigators maintain that oral administration does not give the desired effects in that therapeutic levels cannot be maintained due to the evanescence of the drug.

CONCLUSIONS

1. Tolserol, given intravenously, is a definite diagnostic and prognostic aid in the "acute disc syndrome".

2. Tolserol, by its specific muscle relaxant effect, is effective in the rheumatic and traumatic afflictions of the low back by giving symptomatic relief of pain and spasm, thereby altering the prognosis of these afflictions. Oral administration is effective here, therefore of clinical value.

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