0022-5347/95/1544-1356$03.00/0
THE JOURNAL OF UROLOGY
Vol. 154, 1356–1359, October 1995
Printed in U.S.A.
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EVALUATION OF REAL-TIME RIGISCAN MONITORING IN PHARMACOLOGICAL ERECTION

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ABSTRACT

Purpose: The clinical assessment of pharmacologically induced erectile response was compared to the real-time RigiScan* monitoring response.

Materials and Methods: Erection was induced by 521 intracavernous injections of a new alprostadil formulation. The clinical end point was "full rigidity" and the RigiScan criterion was radial rigidity of 70% or more for 10 consecutive minutes or longer.

Results: For 752 prostaglandin E1 injections the sensitivity and specificity of the RigiScan device compared to clinical evaluation were 53.8% (133 of 247 cases) and 92.9% (469 of 505), respectively. For rigidity of 60% or greater the sensitivity increased to 70.8% (175 of 247 cases) and specificity decreased to 85.0% (429 of 505).

Conclusions: The RigiScan device is useful to document objectively a pharmacologically induced erection yet it appears to be more conservative than clinical evaluation.

KEY WORDS: impotence, penile erection, alprostadil, injections

An objective methodology for testing penile rigidity is the RigiScan ambulatory rigidity and tumescence system. Originally designed for investigation of nocturnal penile tumescence, RigiScan software has been used in sleep laboratories to differentiate between psychogenic and organic causes of erectile dysfunction. Using RigiScan data from more than 500 patients at the Uro-Center of San Diego, Johnson summarized the data obtained from normal findings during RigiScan monitoring, and defined an erection of more than 70% rigidity as sufficient and one of 40 to 70% rigidity as partially sufficient.[1] Others also considered an erection with a rigidity of 70% or more to be a nonbuckling erection and rigidities of less than 40% to represent a flaccid penis.[2] However, rigidity values of less than 70% have been found in normal subjects[3] and have been considered sufficient[4] or adequate.[5] Rigidity has been shown to decrease with patient age.[6]

Recent neurophysiological studies seem to indicate that nighttime erections may be different in neurological input from erections occurring during sexual arousal.[7,8] In contrast, some consider RigiScan monitoring to be an accurate method in other situations, that is in objectively documenting erectile response to intracavernous pharmacological agents.[9] For example, a penile response measurement that incorporated at least 1 phase of 70% rigidity for a duration of at least 5 minutes was used in a study of intracavernous papaverine and phentolamine. Among other intracavernous pharmacological agents used for treatment of erectile dysfunction the naturally occurring prostaglandin E1 (alprostadil) has been extensively studied.[10] During the clinical development of a new prostaglandin E1 formulation, namely alprostadil sterile powder, numerous RigiScan recordings were obtained and erectile response with this objective method was compared to the subjective clinical evaluation of erection. The RigiScan device was selected as an objective noninvasive measure of erectile response because of its suitability for use in multicenter studies with large numbers of patients. The study objectives were to determine the correlation between the 2 methods of erectile response (clinical and RigiScan assessment), and to explore the validity and use of RigiScan methodology in the assessment of pharmacologically induced erection.

Accepted for publication March 24, 1995.
Supported by grants from the Upjohn Company.
Study participants included Drs. Jeffrey Adelglass, Carrollton, Stephen Aronoff and Richard Sachson, Dallas, and William Fitch, San Antonio, Texas; A. Michael Alabaster, Memphis, Tennessee; Ronald G. Anderson, Tacoma and Richard E. Berger, Seattle, Washington; Rodney Appell and Jack Goodman, Gretna, Louisiana; Stephen Auerbach, Newport Beach, Tom F. Lue, San Francisco, Harin Padma-Nathan, Los Angeles and J. Joseph Prendergast, Atherton, California; Richard V. Clark, Durham and Charles Reid, Winston-Salem, North Carolina; Irwin Goldstein, Boston and H. David Mitcheson, Brighton, Massachusetts; Jose Gonzalez, Royal Oak, Michigan; Louis Keeler, Cherry Hill, New Jersey; David Lillie, Kenmore, New York; Thomas Mulligan, Richmond, Virginia; William Patterson, Birmingham, Alabama, and Judy Stone, Cumberland, Maryland.
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MATERIALS AND METHODS

Patient population. Data from 2 multicenter, double-blind, placebo-controlled studies were used. Study 1 was a crossover study in which each patient received a single intracavernous injection of placebo, and 2.5, 5, 7.5 and 10 μg. alprostadil sterile powder in randomized order according to a Latin square design for 5 dose groups. Of 153 patients 23 to 69 years old randomized into the study 128 (83.7%) completed all 5 doses. Study 2 was a fixed single dose, parallel design study in which 296 patients 21 to 74 years old were randomized to 1 of 5 dose groups: placebo (59 patients) or 2.5 μg. (57), 5 μg. (60), 10 μg. (62) or 20 μg. (58) alprostadil sterile powder.

The inclusion criterion for both studies was a history of erectile dysfunction of vasculogenic, neurogenic, psychogenic or mixed etiology (assessed by history, physical examination and routine laboratory studies) at least 4 months in duration. Previous use of intracavernous vasoactive agents was permitted in the crossover study but not in the parallel design study. Exclusion criteria in both studies were anatomical deformation of the penis, penile fibrosis, a history of priapism, recent onset of major diseases or disease states, uncontrolled diabetes or hypertension, major psychiatric disorder, excessive cigarette use and use of other investigational agents. The studies were approved by the institutional review board of each investigator and each patient signed an informed consent form.

Alprostadil sterile powder, the new freeze-dried sterile powder formulation of prostaglandin E1, was specifically developed for use in the treatment of erectile dysfunction. After reconstitution of the sterile powder in 1 ml. sterile bacterio-

static water for injection, the resulting solution is physically and chemically stable for 48 hours at room temperature (25C) or for 7 days under refrigeration (8C) when stored in the original vial.

RigiScan and real-time monitoring. The RigiScan monitoring system has been described previously.[11] At the beginning of the studies, it was expected that the RigiScan data would be processed using the nocturnal mode to collect pre-injection and post-injection rigidity data. However, analysis of the initial data suggested that this mode was not suitable for provocative testing, such as after intracavernous injection of alprostadil sterile powder. Nocturnal events (erections) in healthy men are cyclic in nature, which means that there is a resting baseline tumescence or an event of some degree in duration that is followed by a return to baseline. During provocative testing, there is no cyclic occurrence of events (that is erections). Accordingly, a real-time package was specifically designed for both studies and implemented by the manufacturer to provide an analysis system suitable for provocative testing. This provocative test used a baseline calculation that was equal to the minimum base tumescence before the initial event mark. The real-time software algorithm allowed for collection of baseline data with use of an event marker at the time of study drug injection to clarify the end of baseline data, as well as use of a personal computer to collect and analyze data at the time it was generated, the feature to which real-time refers. The new real-time software was installed on the RigiScan systems at each study site and the study personnel were thoroughly trained in the technology.

The real-time monitoring system produced printed graphic output from each test session, as well as a printed table of measurements for rigidity and tumescence, which were recorded every 5 minutes. The graph and table were used to determine whether injection of the drug had produced a response (erection), the interval between injection and the start of erection (latency), and the total duration of the erection. In addition to the paper copy of the graph, the data from real-time monitoring were downloaded into a computer file for review using software set in the session scanning mode.

Efficacy measures. The response to an injection of alprostadil sterile powder or placebo was evaluated clinically by the investigator as determined by palpation and observation of the penis, and by central review of the results obtained from RigiScan monitoring. Efficacy evaluations were made at 5, 10, 15, 30, 60 and 120 minutes after injection. The clinical response was graded as full (rigidity sufficient for intercourse), partial (tumescence but not sufficient rigidity for intercourse) or none. A response by clinical evaluation was defined as an erection of full rigidity for at least 1 of the 6 evaluations. The 3 RigiScan end points were: 1) start of erection—the time at which radial rigidity first reached 70% or more at the tip or base of the penis and remained at that level for 10 consecutive minutes or longer, 2) end of erection—the time at which radial rigidity first was less than 70% at the tip and base of the penis, and remained at less than 70% for 10 consecutive minutes or longer and 3) response to injection (erection)—radial rigidity of 70% or more at the tip or base of the penis for 10 consecutive minutes or longer. Several examples illustrating the various types of recordings and their interpretation are shown in figures 1 to 3. Evaluations of the RigiScan data were also repeated using the aforementioned approach but replacing the 70% threshold with 60%.

Statistical methods. Based on response by clinical evaluation and RigiScan monitoring, each injection was classified into 1 of 4 categories as summarized in the Appendix. The sensitivity and specificity of the RigiScan device were calculated under the assumption that the clinical evaluation was a reflection of the true erectile response. The sensitivity estimates the probability of the device detecting an erectile response when a response is truly present according to clinical evaluation. The specificity estimates the probability of detecting no erectile response when there is no response according to clinical evaluation. A high rate of sensitivity indicates that the device often agrees with a clinical evaluation whereas a high rate of specificity indicates that it does not often discern a response when clinical evaluation does not.

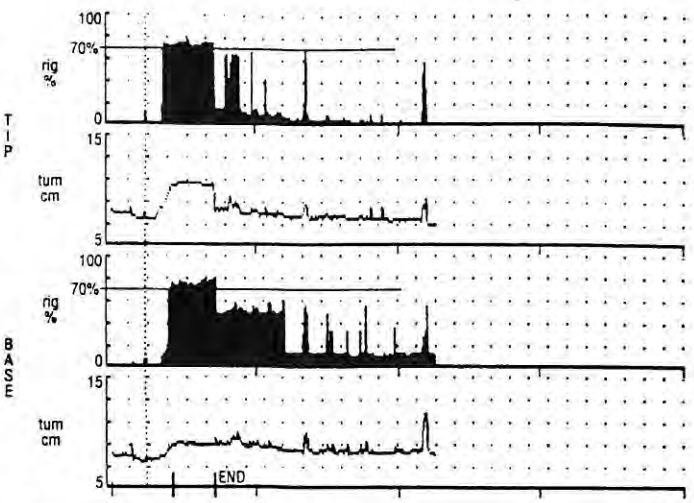

FIG. 1. Response to injection based on RigiScan. Monitoring results are shown from session during which patient experienced increases in tumescence (*tum*) at base and tip of penis immediately after injection, with corresponding increases in rigidity (*rig*). Rigidity at base increased to 70% within 11 minutes after injection and remained greater than 70% for 17 minutes. At that time, rigidity decreased to less than 70% and remained near 50% for approximately 30 minutes. Rigidity at base then fluctuated at approximately 10% for approximately 60 more minutes and then decreased to zero. Session reflects response based on RigiScan with erection starting at 11 minutes and ending at 28 minutes. Thus, latency was 11 minutes and duration was 17 minutes.

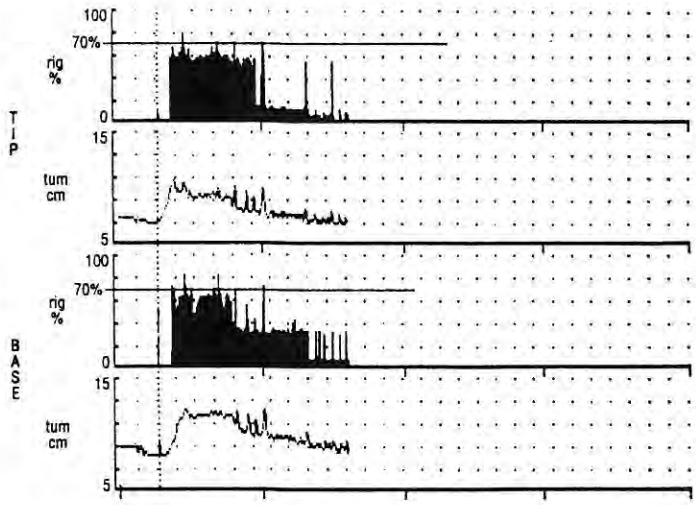

FIG. 2. Good clinical response to injection but inadequate or partial response based on RigiScan. Monitoring results are shown from session during which patient had increases in tumescence (*tum*) at base and tip of penis, with corresponding increases in rigidity (*rig*) at both sites. Rigidity at base and tip fluctuated at approximately 60% for almost 1 hour but was measured to be more than 70% at only few time points. This session represented good clinical response to treatment even though rigidity was not greater than 70% for 10 consecutive minutes, and was interpreted as no response to treatment based on RigiScan data.

RESULTS

Crossover study. Clinical evaluation and RigiScan data were available for 521 injections of alprostadil sterile powder.

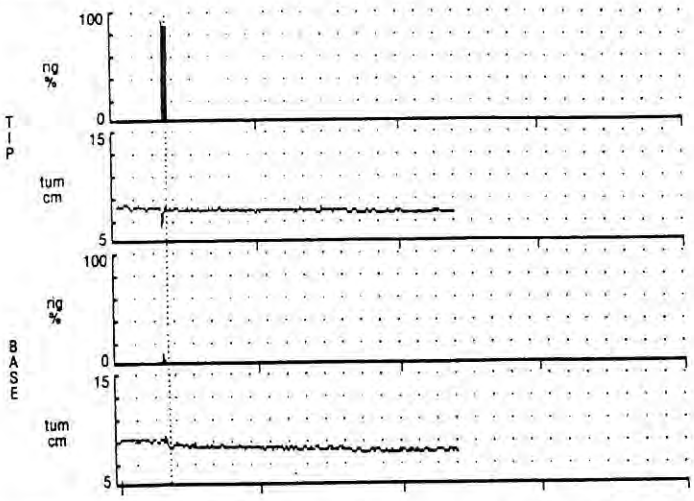

FIG. 3. Results are shown from placebo-treated patient who had no response to treatment. There was no increase in tumescence (*tum*) at either base or tip of penis after injection. Apparent rigidity (*rig*) at tip of penis at injection was artifact, most probably due to manipulation of penis needed for injection.

Placebo injections produced no response by either method in this study and were excluded. The agreement between the 2 methods of assessing erectile response is summarized in table 1.

The erectile response between clinical evaluation and RigiScan methods agreed for 418 of the 521 injections (80.2%). The majority of disagreement was due to the 88 injections (16.9%) for which the erection was judged present by clinical evaluation but not by RigiScan monitoring. The remaining 15 injections (2.9%) produced an erection as assessed by RigiScan criteria but not by clinical evaluation.

The sensitivity and specificity of the RigiScan method compared to the clinical evaluation method were also calculated. The sensitivity, which measures the likelihood that the RigiScan method will identify a response when the clinical evaluation method does, was 47.6% (80 of 168 injections with a clinical response). The specificity, which measures the likelihood that the RigiScan method will not identify a response when the clinical evaluation method does not, was 95.8% (338 of 353 injections with no clinical response).

When the alternative evaluations of the RigiScan data were performed using 60% radial rigidity, rather than 70%, there was agreement for 422 of the 521 injections (81.0%). When the methods disagreed, 59 of 521 injections (11.3%) produced an erection according to clinical evaluation but not by RigiScan monitoring and 40 (7.7%) produced an erection according to RigiScan criteria but not by clinical evaluation. The sensitivity of the RigiScan methodology increased to 64.9% (109 of 168 injections) and the specificity decreased slightly to 92.6% (327 of 353) when the alternative criteria were used.

Parallel design study. Clinical evaluation and RigiScan data were available for the 231 patients who received single, intracavernous injections of alprostadil sterile powder. Of the 59 placebo treated patients none responded by either method and they were excluded from the study. There was agreement in erectile response between the clinical evaluation and RigiScan methods for 184 of the 231 injections (79.6%) (table 2). The majority of disagreement was due to the 26 injections (11.3%) for which erection was judged present by clinical evaluation but not by RigiScan criteria, while in the remaining 21 injections (9.1%) an erection was noted by RigiScan criteria but not by clinical evaluation. The sensitivity was 67.1% (53 of 79 injections with a clinical response) and the specificity was 86.2% (131 of 152 with no clinical response).

When the alternative evaluations of the RigiScan data were performed using 60% radial rigidity, rather than 70%, there was agreement for 182 of the 231 injections (78.8%). When the methods disagreed 13 of 231 injections (5.6%) produced an erection according to clinical evaluation but not RigiScan data and 36 (15.6%) caused an erection by RigiScan criteria but not by clinical evaluation. The sensitivity of the RigiScan methodology increased to 83.5% (66 of 79 injections) and the specificity decreased to 76.3% (116 of 152) when the alternative criteria were used.

DISCUSSION

As early as 1988, some investigators mentioned use of the RigiScan device in a real-time monitoring mode to document efficacy of the pharmacological erection program.[2] Recently, others documented progressively greater response to intracavernous prostaglandin E1 by dose increases using RigiScan real-time monitoring.[12] The response was defined as rigidity of more than 60% for 30 minutes. Another study suggested RigiScan monitoring to be highly accurate for evaluating and documenting objectively the erectile response to intracavernous injection of vasoactive agents, such as papaverine and phentolamine.[9]

Our results clearly differentiated the effectiveness of alprostadil sterile powder relative to placebo. Furthermore, there was acceptable overall agreement between the clinical assessment of erection (full rigidity) and the RigiScan assessment (70% or greater radial rigidity for at least 10 consecutive minutes). The overall agreement between the methods was 80% (602 of 752 alprostadil injections) for both studies, which is based on percent of injections that resulted in the same outcome (response or no response) using both methods. Table 3 displays the agreement of the methods when both studies were combined.

The overall rates of disagreement were 15.2% (114 of 752 injections) for the category of "response by clinical evaluation but not by RigiScan evaluation" and 4.8% (36 of 752) for the category of "response by RigiScan evaluation but not by clinical evaluation." This finding indicates that few injections resulting in 70% or greater rigidity for at least 10 minutes by RigiScan criteria were not judged by the investigator to be a response (that is full rigidity). More injections were judged by the investigator to result in full rigidity based on clinical assessment but that never registered 70% or greater rigidity for 10 consecutive minutes by RigiScan monitoring. When injections for both studies were combined, the overall sensitivity was 53.8% (133 of 247) and the overall specificity was 92.9% (469 of 505).

TABLE 1. *Agreement between clinical evaluation of erection and RigiScan data for the crossover study*

RigiScan Method*	Clinical Evaluation (No. injections)†		
	No Response	Response	Totals
No response	338	88	426
Response	15	80	95
Totals	353	168	521

* Radial rigidity of 70% or more for at least 10 consecutive minutes.
† Full rigidity.

TABLE 2. *Agreement between clinical evaluation of erection and RigiScan data for the parallel group study*

RigiScan Method*	Clinical Evaluation (No. injections)†		
	No Response	Response	Totals
No response	131	26	157
Response	21	53	74
Totals	152	79	231

* Radial rigidity of 70% or more for at least 10 consecutive minutes.
† Full rigidity.

TABLE 3. *Agreement between clinical evaluation of erection and RigiScan data for both studies combined*

RigiScan Method*	Clinical Evaluation (No. injections)†		
	No Response	Response	Totals
No response	469	114	583
Response	36	133	169
Totals	505	247	752

Sensitivity 53.8% (133/247), specificity 92.9% (469/505).
* Radial rigidity of 70% or more for at least 10 consecutive minutes.
† Full rigidity.

These estimates verify the conservative nature of the RigiScan methodology as described and a more moderate definition of response was also evaluated, that is a response by the device was identified if the radial rigidity registered 60% or greater, rather than 70%, for at least 10 consecutive minutes. Table 4 shows the results for the combined studies when this definition of RigiScan response was used. The overall sensitivity was 70.8% (175 of 247 injections with a clinical response) and the overall specificity was 85.0% (429 of 505 injections with no clinical response). The agreement in evaluation remained at 80% (604 of 752 injections). The decrease in specificity indicates that this criterion for identifying a RigiScan response is less strict than that based on 70% rigidity. The overall low response rate to alprostadil sterile powder is due to the lowest dose of alprostadil (that is 2.5 μg.) in both studies and to the low doses of alprostadil (2.5 to 10 μg.) used in the crossover study.

The RigiScan methodology is not without its shortcomings. It is not entirely clear whether there is a good correlation between the radial and axial rigidity as measured by the RigiScan device and application of buckling pressure.[13,14] Also, personnel must be thoroughly trained in the use of this system, otherwise distorted recordings may be obtained. At the start of our experience with the RigiScan system less than optimal results were obtained due to lack of training of study personnel. Only when a full-scale training program, which required repeated use of RigiScan methodology, was instituted did the results improve substantially. Perhaps the low sensitivity established in the studies presented could be explained by errors made by study personnel during recordings. On the other hand, compared with the measurement of axial rigidity, the RigiScan system enables continued monitoring and perhaps is more "user friendly" to the patient. In 1 study buckling device measurements of axial rigidity proved to be highly operator dependent. Furthermore, some patients complained of an unpleasant sensation as the device was applied, which was reflected in a decrease in rigidity.[11]

CONCLUSIONS

Our results indicate overall good correlation between clinical and RigiScan evaluations of erectile response. RigiScan data clearly differentiated alprostadil sterile powder from placebo and, as shown in other studies, established a good dose-response relationship for erectile response.[15] Thus, the RigiScan methodology has a role in pharmacological testing of intracavernous agents.

Cindy L. Shattuck provided technical assistance.

TABLE 4. *Agreement between clinical evaluation of erection and RigiScan data for both studies using the modified definition of RigiScan response*

RigiScan Method*	Clinical Evaluation (No. injections)†		
	No Response	Response	Totals
No response	429	72	501
Response	76	175	251
Totals	505	247	752

Sensitivity 70.8% (175/247), specificity 85.0% (429/505).
* Radial rigidity of 60% or more for at least 10 consecutive minutes.
† Full rigidity.

APPENDIX: CLASSIFICATION AGREEMENT BETWEEN CLINICAL EVALUATION AND RIGISCAN

RigiScan Method	Clinical Evaluation		
	No Response	Response	Totals
No response	Agree	Disagree	No RigiScan response
Response	Disagree	Agree	RigiScan response
Totals	No clinical response	Clinical response	Totals

Injections were classified according to response by each method.

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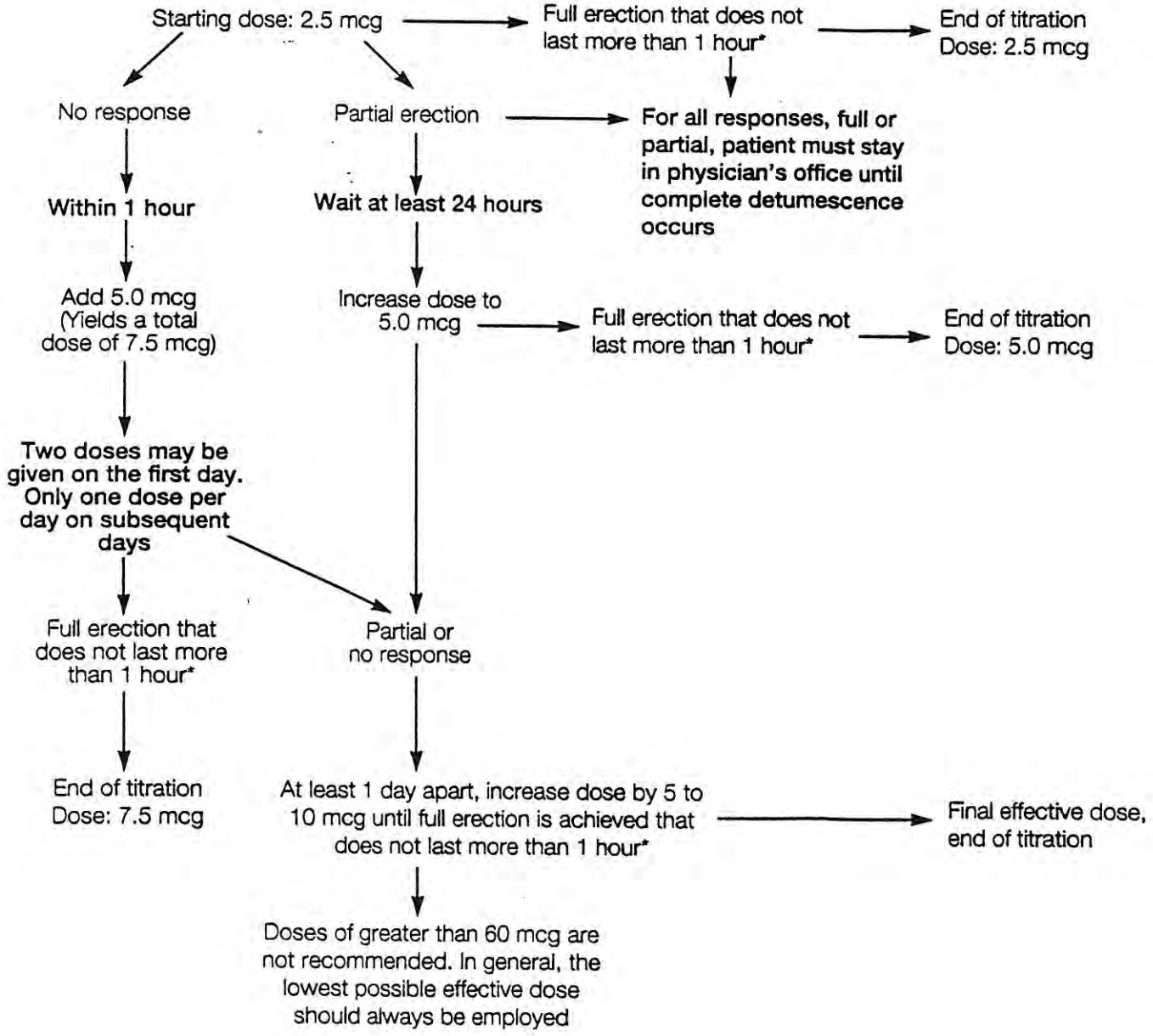
Caverject Sterile Powder
alprostadil for injection

Dosage Titration Guidelines

Erectile Dysfunction of Vasculogenic, Psychogenic, or Mixed Etiology

The dose of CAVERJECT should be individualized for patients by careful titration under supervision by the physician.



Underlying, treatable medical causes of impotence should be diagnosed and treated before therapy with CAVERJECT is initiated.

* If the duration of erection exceeds 1 hour, the dose of CAVERJECT should be reduced.