

Tamsulosin and risk of priapism: A causality assessment using Austin Bradford Hill Criteria

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Funding information

No funding was used to carry out this investigation.

Abstract

Tamsulosin hydrochloride, a selective alpha-adrenergic blocking agent has been previously associated with priapism. Priapism is a medically serious condition that, if not intervened, can cause permanent erectile dysfunction. This study was conducted to investigate whether the association of tamsulosin and priapism is causal. All currently available evidence such as experimental, biological, toxicological, published studies, and safety data mined from the WHO global pharmacovigilance database was systematically organized into the Austin Bradford Hill causality assessment framework. In the international pharmacovigilance database, a strong association between tamsulosin and priapism ($IC_{025} = 4.1$; $PRR_{025} = 19.9$; $ROR_{025} = 20$) was observed. There were 122 cases of priapism associated with tamsulosin submitted to the database from 23 countries. In 87.7% of the cases, tamsulosin was reported as a 'sole suspect,' and in 50.8%, it was the only drug administered. In several patients, priapism resolved following discontinuation of tamsulosin and recurred after its reintroduction. Both in the published and unpublished data, for majority of the cases, the time to onset of priapism was within few days following the first intake of tamsulosin. Cases of priapism, particularly those published, were consistent in their clinical features with patients experiencing prolonged painful erection that required aspiration of cavernosal blood, irrigation of the corpora cavernosa, and treatment with vasopressors. Other alpha-adrenergic blocking agents that are structurally analogous with tamsulosin have also been associated with priapism. In several cases, tamsulosin was used off-label, for the treatment of ureteral calculi expulsion. Eight patients experienced priapism that ended up with serious complications such as ejaculation disorders and erectile dysfunction. The currently available totality of evidence suggests that the association of tamsulosin and priapism is causal. Healthcare professionals are therefore recommended to cautiously prescribe tamsulosin and ensure that consumers are aware of the potential risk of priapism.

Abbreviations: BPH, benign prostatic hyperplasia; LUTS, lower urinary tract symptoms; MedDRA, Medical Dictionary for Regulatory Activities; ROR, reporting odds ratio; SmPC, summary of product characteristics.

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KEYWORDS

association, Austin Bradford Hill criteria, causation, priapism, tamsulosin

1 | INTRODUCTION

Tamsulosin hydrochloride, a selective alpha-1A and alpha-1B adrenoceptor antagonist, has been previously associated with priapism or prolonged and painful erection. Priapism is a pathological condition of penile erection that persists for more than 4 h, which is not associated with sexual desire or stimulation.¹ If not intervened, priapism could be medically serious and can cause permanent erectile dysfunction.² In the medical literature, there were only published single case reports except for one article that documents two cases associating tamsulosin and priapism.³⁻¹⁵ The association might be attributed to the previously published case reports as there were no published epidemiological studies.

According to the summary of product characteristics (SmPC) of tamsulosin, priapism associated with the drug has been reported as 'very rare'; occurring in frequencies between less than 1 in 50 000¹⁶ and 1 in 10 000 users.¹⁷ Tamsulosin is indicated for the treatment of signs and symptoms of lower urinary tract symptoms (LUTS) associated with benign prostatic hyperplasia (BPH). The general background incidence rate of priapism, that occurs in all age groups, was estimated to be 0.5 to 0.9 cases per 100 000 person-years.¹ Although idiopathic cases of priapism are the most frequent, accounting for nearly 50% of all reported cases, drug-induced priapism occurs in 30% of reported cases, rendering it common as well.¹⁸ Associations between one or more variables are usually made based on temporality, causality at the individual level, expert judgment, and/or statistical inferences. Thus, further investigations are required to explore if the reported association can be causal.

Currently, published studies that explored whether this association could be causal are not available. There are only single case reports recorded for this association. Triggered by a single locally reported case that ended up with erectile dysfunction, this investigation was carried out by the Eritrean Pharmacovigilance Centre to assess the causal link between tamsulosin and priapism. The assessment of causality was guided by the Austin Bradford Hill criteria using the publicly available information including preclinical, clinical, and epidemiological data as well as by analyzing the WHO global pharmacovigilance database.¹⁹

2 | MATERIALS AND METHODS

2.1 | Study design

This was a descriptive analysis that evaluated the likelihood of the causal relationship between tamsulosin and priapism using Austin Bradford Hill criteria or guidelines. Hill's criteria are a causality assessment framework developed in 1965²⁰ and adopted

for application in pharmacovigilance and pharmacoepidemiology in 2002.²¹ All available published and unpublished data were incorporated into this causality assessment framework to enable that the evaluators assess causality at the population level based on the totality of evidence available in the medical literature. The Bradford Hill criteria used for judging the evidence of causality include strength of association, temporal relationship, consistency of the association, plausibility (biological, pathological or pharmacological mechanism), dose-response relationship, experimental evidence (including positive dechallenge and rechallenge information), specificity of the cases, coherence, and analogy. Cases that were suspected to have other alternative explanations such as potential confounders were not included into the causality assessment framework.

2.2 | Exposure and outcome definition

The main exposure of interest in this study was tamsulosin tablet used at varying doses with or without other concomitant drugs. The primary outcome measure was the development of priapism, which is defined as a painful penile erection that is unrelated to sexual stimulation and lasts for at least 4 h.¹

2.3 | Literature search and labelling

Available unpublished and published information such as preclinical, clinical, epidemiological, biological, and toxicological data were explored and organized into the causality assessment framework to decide based on the totality of evidence. Literature search was made in Google Scholar, Scopus, Embase, OpenGrey and PubMed/Medline using the following search terms: "priapism" or "painful penile erection" or "prolonged erection" or "induced priapism" and "tamsulosin". The search was performed by YF and MR in the first week of November, 2020. Relevant articles from the bibliographical list of available studies that meet the eligibility criteria were included. All articles that directly associated tamsulosin with priapism were included in this study, whereas studies that described other possible alternative explanations or confounders for the occurrence of priapism were excluded. Selection of the eligible articles and their analysis was carried out by all authors. Summary of product characteristics and prescribing information of tamsulosin approved by major regulatory authorities were also reviewed to check whether the causal association of priapism and tamsulosin was documented. Furthermore, online adverse drug reaction databases such as Martindale: the complete drug reference,²² SIDER side effect resource,²³ and Drugdex²⁴ were also explored.

2.4 | Data mining approach

The WHO global database of ICSRs, VigiBase, was used as one data source. VigiBase is the world's largest pharmacovigilance database, which is developed and maintained by the Uppsala Monitoring Centre on behalf of the WHO.¹⁹ The database has been pooling safety data of medical products from different countries since 1968, and during data mining (Nov 01, 2020), it had over 23.5 million ICSRs. The main reason for the data mining was to capture information on the temporal relationship, strength of association, consistency of the cases, dechallenge and rechallenge, dose–response relationship, and the causal relationship of tamsulosin and priapism at individual level. ‘Tamsulosin’ as an active ingredient and ‘priapism’ as MedDRA (Medical Dictionary for Regulatory Activities) preferred reaction term were used as search criteria in VigiLyze, a data mining and analysis tool of VigiBase. Based on the search criteria, both qualitative and quantitative information was retrieved. During data mining, the database was set at ‘de-duplicate’ to automatically remove all suspected/potential duplicates from the analysis. From the quantitative analysis, measures of strength of association such as reporting odds ratio (ROR), proportional reporting ratio (PRR) and/or information component (IC value) as well as cases with single suspect, number of reporting countries, cases with positive dechallenge and rechallenge, etc., were obtained. ROR, PRR, and IC values are measures of association in the database. The qualitative data was exported to excel spreadsheets for descriptive analysis. In the excel spreadsheet, time to reaction onset (calculated as the difference between date priapism occurred and date of tamsulosin intake started), cases of priapism encountered with the sole administration of tamsulosin, outcome of priapism, median age, etc., were identified. Furthermore, efforts were made to identify cases having best evidence of causality (probable or certain), such as those that occurred following the sole intake of tamsulosin, had no alternative explanation, recovered with withdrawal of tamsulosin and experienced the reaction after re-introduction of the drug.

2.5 | Case assessment

The causal relationship of all published case reports of tamsulosin and priapism were also assessed using the Naranjo adverse drug reaction probability scale.²⁵ After exploring the totality of evidence, based on both published and unpublished data, causality at the aggregate level was carried out using Austin Bradford Hill causality assessment framework.²¹

3 | RESULTS

3.1 | Literature search and labelling

Literature search, in the abovementioned databases, was performed in the first week of November, 2020. The search found 13 published case reports that associate tamsulosin with priapism.^{3–15} One article

was, however, excluded as the case could be explained by another alternative cause (had a potential confounder). The rest 12 published papers comprising 13 single case reports were hence subjected to further evaluation (Table 1). In the literature analysis, six of the 13 case reports demonstrate that tamsulosin was taken for benign prostatic hyperplasia. In the rest seven cases, tamsulosin was used off-label: for the management of renal calculi in four cases, for obstructive voiding symptoms in two cases, and for unspecified lower urinary tract symptoms in one case. In all cases, tamsulosin was used within the recommended dose. The time to reaction onset, for cases where it was documented, was within a few days following the commencement of tamsulosin, and in one case, it was manifested after 2 years. The duration of priapism, from onset to recovery, was reported to be from 6 h to 72 h. Outcome was documented in all case reports, and it was reported that all patients had recovered, except in one case that failed to resolve even with surgical intervention.

Priapism was first associated with tamsulosin in a case report that was published in 2003 by Dodds et al.⁹ The reaction was nevertheless previously associated with prazosin²⁶ as well as doxazosin and terazosin,²⁷ which lie within the same therapeutic class as tamsulosin. Apart from these case reports, there were no epidemiological, clinical, and preclinical studies that associate priapism with tamsulosin. Moreover, the association was not documented in online adverse effect databases—Martindale, SIDER side effect resources, and Drugdex. It was, however, documented in the summary of product characteristics or in the prescribing information of tamsulosin approved by the Medicines and Healthcare Products Regulatory Agency (MHRA)/European Medicines Agency (EMA), and US-FDA.^{16,17}

3.2 | Results of causality assessment

In nine cases, priapism resolved following discontinuation of tamsulosin (positive dechallenge), and in one case, it recurred after re-introduction of the product (positive rechallenge) (Table 1). Upon causality assessment, priapism was found to be ‘probably related’ in 11 cases, ‘possibly related’ in one case, and ‘certainly related’ in another case.

3.3 | Reports in the WHO global database of individual case safety reports, VigiBase

Since 1998, a total of 122 cases of priapism associated with tamsulosin were submitted from 23 countries to the global database, VigiBase. The cases were mainly reported from the US, the UK, Canada, Spain, France, and the Netherlands. Of the cases with documented source of primary reporters (101/122), 63% were reported by physicians and 17.8% were from non-healthcare professionals. The rest, 17.5%, were submitted by pharmacists and other healthcare professionals. The disproportionality measures or the measures of association between tamsulosin and priapism in

TABLE 1 Summary of the published case reports of tamsulosin associated with priapism as of November 1, 2020

| Case report | Age (years) | Daily dose (mg) | Concomitant medicines | Duration | Indications | Time to onset | Action taken | Dechallenge/Rechallenge | Outcome |
|--|-------------|-----------------|---|----------|---------------------------------------|---------------|---|-------------------------|------------------------|
| Marconi et al. (2019) ³ | 45 | 0.4 | Ketorolac | 6 h | Renal colic | 2 days | Phenylephrine injected directly into cavernosa | +/UK | Recovered |
| Prihadi et al. (2020) ⁴ | 57 | 0.4 | ACE inhibitors, beta blockers & statins | 72 h | LUTS | – | Distal aspiration and irrigation procedure | +/UK | Recovered |
| Spagnul et al. (2011) ⁶ | 32 | 0.4 | None | 40 h | Urinary urgency and enlarged prostate | 1 day | Aspiration of the corpora and intracavernosal injection of 1:1000 adrenalin solution | +/UK | Recovering |
| Pahuga et al. (2004) ⁷ | 56 | 0.4 | None | 28 h | BPH | 2 weeks | Aspiration and intracavernosal irrigation of iced saline and vasoconstrictive agent. Then winter procedure performed but all failed and priapism persisted. | UK/UK | Not yet recovered |
| Cosentino et al. (2014) ⁵ | 67 | 0.4 | None | 12 h | BPH | 3–4 weeks | Intracavernosal injection of vasoconstrictor was performed and ultimately irrigation corpora cavernosa with saline solution | +/UK | Recovered |
| Kilinic et al. (2008) ⁸ | 59 | 0.4 | None | 2 days | LUTS | 2 days | Irrigation of the corpus cavernosum and a proximal corpus cavernosal–spongiosum shunt performed. | UK/UK | Recovered |
| Dodds et al. (2003) ⁹ | 58 | 0.4 | Hydrochlorothiazide | 7 h | Obstructive voiding symptoms | 4 days | Corporeal irrigation with saline and phenylephrine. | +/+ | Recovered |
| Venyo et al. (2010) ¹⁰ | 35 | 0.4 | Diclofenac, paracetamol and tramadol | 7 h | Ureteric colic or renal calculi | 1 day | Blood aspirated from his corpora cavernosa | +/UK | Recovered |
| Hammond et al. (2014) ¹¹ | 44 | 0.4 | XX | 3 days | BPH | 9 days | Unsuccessful attempts were made to irrigate and inject with phenylephrine to achieve detumescence | +/UK | Recovering |
| Khater et al. 2020 ¹² | 61 | 0.8 | None | 18 h | LUTS | 1 day | Aspiration, irrigation, and phenylephrine injection | UK/UK | Recovered |
| | 24 | 0.4 | Propofol | 7 days | Renal or ureteral stone | 8 h | Aspiration and irrigation with intracorporeal injections of phenylephrine | +/UK | Recovered with sequale |
| De bruin D et al. (2008) ¹⁴ | 47 | 0.4 | Missing | Missing | Ureteral stone | – | | UK/UK | Unknown |
| Kariyanna (2015) ¹⁵ | 71 | 0.8 | Aspirin, ticagrelor, statins, enalapril, nitroglycerin, insulin and metformin | 16 h | BPH | – | Phenylephrine injection | +/UK | Recovered |

Abbreviations: +, Positive; LUTS, Lower Urinary Tract Symptom; UK, Unknown; XX, Efavirenz/emtricitabine/tenofovir disoproxil, boceprevir, peginterferon alfa-2b, ribavirin, doxazosin, tamsulosin, quetiapine, testosterone cypionate, ondansetron, esomeprazole, lithium, losartan, naproxen, acetaminophen/oxytocodone, loperamide, codeine/guafenesi, cyclobenzaprine.

VigiBase was found to be $IC_{025} = 4.1$; $PRR_{025} = 19.9$; $ROR_{025} = 20$. In 87.7% of the cases, tamsulosin was marked as a 'sole suspect,' and in 50.8%, it was reported as the only drug administered. In 42 cases, priapism resolved following the discontinuation of tamsulosin (positive dechallenge), while in two cases, it recurred after the product was reintroduced (positive rechallenge). Out of the 42 cases with positive dechallenge, 22 cases took tamsulosin only without other concomitant drugs, and in 18 cases, it was the only suspected drug among all the rest received. Of the cases with positive rechallenge, tamsulosin was the sole drug taken in one case, and in the rest, it was a sole suspect.

Subgroup analysis was performed for the cases associating priapism with the sole administration of tamsulosin (62/122). The median time to the onset of priapism, where reported, was one day (range: 1 to 6 days) following the first intake of tamsulosin. In 22.5% of the cases, priapism was marked as 'resolved' after the discontinuation of tamsulosin. Outcome was reported in only in 36 out of the 62 cases. Of the 36 cases, 25 were documented as recovered and/or recovering, while the rest 11 cases had not recovered by the time of reporting. In the rest of the cases, outcome of priapism was not reported or documented. In eight patients, it was reported that priapism had ended up with serious complications; six ejaculation disorders and two erectile dysfunctions.

The summary results of each criterion of the Austin Bradford Hill causality assessment are presented in Table 2.

4 | DISCUSSION

4.1 | Strength of the association

The association of priapism and tamsulosin, based on the calculated IC value, ROR and PRR, was found to be very strong. The IC value is a measure of the disproportionality of a drug–adverse drug reaction pair in VigiBase.²⁸ A positive IC_{025} value (the lower border of the credible interval for the IC value >0) is “a traditional threshold which indicates that a drug-ADR pair is reported more often than expected based on all reports in the database”, thus, showing a statistical signal.

4.2 | Temporal relationship

The short time to onset, within few days, of priapism following the first intake of tamsulosin both in the cases retrieved from the WHO global database and the published case reports indicates temporal plausibility of the association and, thus, supports causation.

4.3 | Consistency of the association

For the association to be consistent, different studies and/or reports conducted in different places of the world should come up

TABLE 2 Summary results of the causality assessment of tamsulosin and priapism using Hill's criteria

| Criterion | Result | Remarks |
|---|--------|---|
| Was the association strong? | Yes | $IC_{025} = 4.1$; $PRR_{025} = 19.9$; $ROR_{025} = 20$ all suggest a strong association |
| Was the temporality plausible? | Yes | In cases where time to onset is documented, priapism has been manifested shortly following administration of tamsulosin; with a median of 2–3 days. |
| Was the association consistent? | Yes | Different cases of priapism with similar clinical features have been reported from different parts of the world. |
| Was there a dose-response relationship? | No | No specific studies exploring dose-response relationship were found. Available evidence is not sufficient to conclude on this criterion. |
| Were there experimental evidences suggesting the association? | Yes | In several cases, priapism resolved following discontinuation of tamsulosin and recurred after re-administration of the product. |
| Was the association specific? | Yes | In majority of the cases, priapism was encountered following sole intake of tamsulosin. |
| Is there a plausible mechanism for the association? | Yes | Tamsulosin, as a selective α_1 -receptor blocker, might cause priapism through inhibition of sympathetic effects which are necessary for the de-tumescence of the penis. |
| Are there analogies that explain a similar association? | Yes | Other alpha-adrenergic blocking agents structurally analogous with tamsulosin have been associated with priapism. |
| Are the findings in coherence with the established knowledge? | Yes | Alpha-adrenergic blocking agents have been associated with penile erection and thus, priapism might be an exaggerated effect. |

Abbreviations: IC, information component; PRR, proportional reporting ratio; ROR, reporting odds ratio.

with similar conclusions or observations. As there were no published epidemiological studies, we only considered published case reports and ICSRs submitted to the WHO global database, VigiBase. In many of the cases reported to VigiBase, the time to onset, clinical features and outcome of priapism showed similar clinical patterns. Several of the published case reports manifested within few days after the intake of tamsulosin and recovered shortly after 1–3 days following its discontinuation. In the majority of the published case reports, there was a prolonged painful erection that required aspiration of cavernosal blood, irrigation of the corpora cavernosa with saline solution, and administration of intracavernosal injection with phenylephrine or adrenaline. Besides, the fact that cases were reported from more than 20 countries indicates a geographic distribution of the problem. These repeated and/or consistent observations across several countries strengthen the causal inference.

4.4 | Specificity of the association

Specificity explores how specific the exposure and the outcome of interest are. When a specific outcome is being associated with a specific exposure, we conclude that the criterion is met. This means that one thing should not be associated with many things. Since diseases or adverse effects can have multiple etiologies and therapies can have multiple effects, specificity is often inconclusive and is comparatively a weaker criterion. In this study, the fact that majority of the cases of priapism, both the published and those retrieved from VigiBase, were reported with the sole administration of tamsulosin and without other possible alternative explanations, reflects that the association was specific in terms of the exposure of interest. On the other hand, the fact that a significant proportion of the cases report priapism as the only reaction suggests that the association was specific in terms of the outcome of interest as well.

4.5 | Biological plausibility

A proposed mechanism for priapism is probably through the inhibition of sympathetic effects, which are necessary for the transduction of impulses of detumescence of the penis. Such inhibition may actually result from the blockade of alpha-receptors (especially α_1 -receptor) by drugs such as tamsulosin.^{4,6}

Penile erection and detumescence are regulated through the relaxation and contraction of the smooth muscles of both the cavernosal sinus spaces and the arteriolar tree within the penis. Because of the contraction of the sinuses and arterial branches, the resistance to blood flow into the penis is generally high in the flaccid state. Tamsulosin as a selective alpha-blocker with the effect on prostate and corporal smooth muscle can cause the smooth muscles to relax and minimize resistance to incoming blood flow into the penis, thereby causing penile erection.^{29,30} The observation of cases

of priapism in patients taking tamsulosin could therefore be interpreted as an extreme end of a spectrum of manifestations resulting from decreased resistance to the flow of blood into the penis. This is a documented effect that strongly goes in favor of the association between tamsulosin and priapism.

4.6 | Experimental evidence

Animal studies, clinical trial experiences, and reported information on positive dechallenge and rechallenge were considered for evaluation of this criterion. Experimental evidence, where available, is among the most compelling evidence for causation. Even though evidence from animal studies was lacking in this case, several published and unpublished cases demonstrated that priapism resolved following discontinuation of tamsulosin and recurred after readministration of the product, which supports the causation. This is technically and logically a sort of unintended experimentation.

4.7 | Dose–response relationship

So far, there are no studies that explored the dose–response relationship of tamsulosin and priapism. Besides, in all of the cases including both the retrieved and published ones, where dose of tamsulosin was reported, there was no issues of overdose except in one case. Thus, more information is required to conclude on this criterion.

4.8 | Analogy

According to the modified Hill's viewpoints, products that are structurally analogous are expected to exert similar effects. In our case, other alpha-adrenergic blocking agents such as prazosin, terazosin, doxazosin, and alfuzosin, which are drugs of the same class and are structurally analogous with tamsulosin, have been associated with priapism, which supports the association.^{27,31}

4.9 | Coherence

Alpha-adrenergic blocking agents are expected to cause normal penile erection,³² and priapism is just one extreme within the spectrum of the expected effects.

4.10 | Weighing the overall evidence

In summary, the strong association observed, the plausible temporal relationship, the repeated observation of clinically similar cases from several countries, the suggested biological mechanism, occurrence of majority of the cases with the sole administration of tamsulosin, having several cases with positive dechallenge and rechallenge as

well as the existing analogy and coherence together support a possible causal relationship between tamsulosin and priapism (Table 2). This causal inference, however, is tentative, and judgments are made on the basis of the available evidence. In Hill's criteria, temporal relationship is the only absolutely essential criterion, and the greatest weight are then given to biological plausibility, consistency, and the dose–response relationship.³³ In our study, except the dose–response relationship, all other criteria were fulfilled, and the likelihood of the causal relationship is heightened as the overall available evidence lead to the same conclusion.

The strength of this study is that the possibility of causation was systematically examined using the viewpoints developed by Austin Bradford Hill, which is believed to be rigorous in assessing a causal link between an outcome and exposure. Reversibility/outcome and seriousness of priapism were not documented or reported in several cases, which requires further studies.

5 | CONCLUSION

The currently available totality of evidence on the strength of association, temporality, consistency, specificity, experimental evidence, biological plausibility, analogy, and coherence suggests that the association of tamsulosin and priapism is causal. This causal association is medically important as it has serious implication in clinical practice. In many of the cases, surgical intervention was required to manage the reaction, while in some cases, the reaction ended up with serious complications such as ejaculation disorders and erectile dysfunction. Healthcare professionals are therefore recommended to cautiously prescribe tamsulosin and ensure that benefits outweigh risks when using the drug, and consumers are aware on the associated risk.

DISCLOSURE

The authors declare that they have no competing interests.

AUTHORS' CONTRIBUTION

All authors made a significant contribution from the conception to the write-up of the manuscript. YF and MR did the literature search and all authors participated in the analysis of literature. All authors gave final approval of the last version of the manuscript to be published.

ETHICS APPROVAL AND CONSENT FOR PUBLICATION

Not applicable.

DATA AVAILABILITY STATEMENT

Data used for this report are all available in this article.

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How to cite this article: Russom M, Fitsum Y, Debesai M, Russom N, Bahta M. Tamsulosin and risk of priapism: A causality assessment using Austin Bradford Hill Criteria. *Pharmacol Res Perspect.* 2022;10:e00934. doi:[10.1002/prp2.934](https://doi.org/10.1002/prp2.934)