

# Confirmation of Ureteric Patency During Cystoscopy Using Phenazopyridine HCl: A Low-cost Approach

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## Abstract

**Objective:** To describe the use of oral phenazopyridine (Pyridium) prior to pelvic surgery to facilitate intraoperative confirmation of ureteric patency.

**Materials and Methods:** We performed a chart review of women given phenazopyridine preoperatively prior to pelvic surgery in a tertiary care centre between July 2004 and June 2005. The primary outcome was the cystoscopic observation of bilateral ureteric urine efflux. Secondary outcomes included the visualization of bladder mucosa during cystoscopy, postoperative complications, and urinary tract injury diagnosed postoperatively (i.e., missed intraoperatively).

**Results:** Pelvic reconstructive surgery requiring intraoperative cystoscopy was performed in 124 women. Bilateral ureteric patency and bladder mucosal integrity was confirmed in all cases. Phenazopyridine was well tolerated by all patients, and its use was unequivocally documented in 32 subjects whose chart was reviewed to determine postoperative course. Bladder mucosal appearance was unaltered. Dye continued to be excreted during prolonged procedures. Postoperatively, no ureteric injuries were subsequently diagnosed in any patients. The cost per patient of phenazopyridine (\$0.29) is substantially lower than indigo carmine (\$34.50).

**Conclusion:** Preoperative oral phenazopyridine is an inexpensive and safe dye that assists effectively in the confirmation of ureteric patency when cystoscopy is planned during pelvic surgery.

## Résumé

**Objectif :** Décrire l'utilisation de la phénazopyridine (Pyridium) par voie orale avant la tenue d'une chirurgie pelvienne afin de faciliter la confirmation peropératoire de la perméabilité urétérale.

**Documents et méthodes :** Nous avons mené une analyse des dossiers des femmes qui se sont vu administrer de la phénazopyridine avant la tenue d'une chirurgie pelvienne au sein d'un centre de soins tertiaires entre juillet 2004 et juin 2005. L'observation cystoscopique d'un flux urinaire sortant urétéral bilatéral constituait le critère d'évaluation principal. Parmi les

critères d'évaluation secondaires, on trouvait la visualisation de la muqueuse vésicale au cours de la cystoscopie, les complications postopératoires et les lésions du tractus urinaire diagnostiquées après l'opération (c.-à-d. celles qui sont passées inaperçues pendant l'opération).

**Résultats :** Une chirurgie de reconstruction pelvienne nécessitant une cystoscopie peropératoire a été menée chez 124 femmes. La perméabilité urétérale bilatérale et l'intégrité muqueuse vésicale ont été confirmées dans tous les cas. La phénazopyridine a été bien tolérée par toutes les patientes et son utilisation a été clairement documentée chez 32 sujets dont le dossier a été analysé afin de déterminer l'évolution postopératoire. L'apparence de la muqueuse vésicale est demeurée inchangée. Le colorant continuait d'être excrété au cours des interventions prolongées. À la suite de l'opération, aucune lésion urétérale n'a été subséquentement diagnostiquée chez l'une ou l'autre de ces patientes. Le coût par patiente de la phénazopyridine (0,29 \$) est substantiellement inférieur à celui du carmin d'indigo (34,50 \$).

**Conclusion :** La phénazopyridine administrée par voie orale avant l'opération constitue un colorant abordable et sûr qui contribue efficacement à la confirmation de la perméabilité urétérale, lorsque la tenue d'une cystoscopie est prévue dans le cadre d'une chirurgie pelvienne.

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## INTRODUCTION

Pelvic reconstructive procedures carry a significant risk of ureteric injuries, and routine intraoperative cystoscopy has been shown to reduce the risk of ureteric injury from 5.9% to less than 1%.<sup>1</sup> Cystoscopic confirmation of patency is often facilitated with an intravenous dye, typically indigo carmine (which stains the urine blue).<sup>2,3</sup>

Between July 2004 and June 2005, indigo carmine became temporarily unavailable in Canada because of manufacturing and distribution issues, so an alternative dye was needed. Methylene blue was considered, but it is not an ideal agent. Most of the dye is excreted as a colourless metabolite, leukomethylene blue,<sup>4</sup> limiting clear visualization of efflux. Methylene blue can also interfere with patient pulse oximetry, altering light absorption, transiently artificially lowering oxygen saturation level readings.<sup>5,6</sup>

**Key Words:** Cystoscopy, pelvic floor surgery, urinary incontinence, stress/surgery, urinary incontinence, stress/complications, phenazopyridine, ureter injuries

Competing Interests: None declared.

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**Table 1. Characteristics of patients receiving intraoperative cystoscopies with phenazopyridine**

Clinical characteristics (n = 32)	Mean (SD)	n (%)
Age	52.5 (12.5)	
BMI*	28.2 (5.1)	
Parity		
0		1 (3.1)
1		2 (6.3)
2		17 (53.1)
3		10 (31.3)
≥ 4		2 (6.3)
Menopausal status†		
Premenopausal		9 (32.1)
Perimenopausal		3 (10.7)
Postmenopausal		16 (57.1)
Prior hysterectomy		18 (56.3)
Previous urogynaecologic surgery*		12 (38.7)
Pelvic reconstructive surgery‡		6 (19.4)
Anti-incontinence surgery		11 (35.5)
Index surgery*		
Pelvic reconstructive surgery		16 (51.6)
Anti-incontinence surgery		28 (90.3)

\*Data missing for 1 patient  
†Data missing for 4 patients  
‡A given patient may have undergone multiple procedures

The use and safety profile of oral phenazopyridine (Pyridium, Pfizer Canada) as a bladder analgesic is well established when used for a single short course (200 mg 3 times daily for 2–3 days). Within one hour after oral ingestion of phenazopyridine, the urine acquires a characteristic orange tint. A Medline search of the terms phenazopyridine (1966–2006), aminopyridines (1979–1990) and pyridines (1975–1978) (subheadings: adverse effects, poisoning, toxicity) identified no complications occurring with use of the recommended dose in a single short course. Chronic use,<sup>7</sup> sometimes for as little as 10 days in the elderly,<sup>8</sup> frequently repeated two or three day courses using the recommended dosage,<sup>9</sup> acute overdose,<sup>10</sup> and use in patients with enzymatic deficiencies (glucose-6-phosphate dehydrogenase,<sup>11</sup> NADH-methemoglobin reductase<sup>12</sup>) or with renal insufficiency<sup>13</sup> have all been associated with serious complications. These include methemoglobinemia, sulfhemoglobinemia, acute renal failure, hemolytic anemia and hypersensitivities.<sup>14</sup>

The aim of this study was to report our experience with use of oral phenazopyridine as an alternative to indigo carmine and methylene blue, and to demonstrate the feasibility of using it to confirm ureteric patency during intraoperative

cystoscopy in patients undergoing pelvic reconstructive surgery.

## MATERIALS AND METHODS

This observational retrospective case series included all female patients who underwent anti-incontinence or prolapse reconstructive surgery at Kingston General Hospital, a tertiary level centre, performed between July 2004 and June 2005 by two of the authors (MAH, SLJ). Only those subjects who had confirmed administration of phenazopyridine preoperatively were included in the chart review evaluating the safety and effectiveness of phenazopyridine use. No patients were excluded from the analysis.

Women received a single oral dose of phenazopyridine (100–200 mg) one hour preoperatively with a sip of water. The surgery was performed using standard technique. Immediately prior to intraoperative cystoscopy, the bladder was emptied, filled retrograde with 300 cc of sterile saline, drained to flush dye, and refilled with 300 cc of saline. The mucosa was inspected for bladder integrity and ureteric patency was confirmed by the visualization of a bright orange (at times reddish) jet of urine expelled from each ureteric orifice.

The primary outcome for the study was the cystoscopic observation of phenazopyridine-stained urine efflux from each ureteric orifice, confirming ureteric patency. The cystoscopic visualization of the bladder mucosa integrity was a secondary outcome. Other secondary outcomes included the documentation of possible complications from phenazopyridine administration (allergic reaction, unexplained intraoperative hypotension). Any urinary tract injury diagnosed postoperatively (i.e., the diagnosis was missed intraoperatively) was recorded. This information was gathered by reviewing the subject's hospital records, including any postoperative hospital admissions, local emergency room visits and from any investigations (e.g., imaging) or treatment (e.g., ureteric reimplantation) carried out thereafter. The absence of postoperative urinary tract injury was used as a measure of the efficacy of intraoperative phenazopyridine use.

Descriptive statistics were reported on age, parity, BMI, past urogynaecologic surgeries, and current surgery. The outcomes were described as proportions. The mean and standard deviation or numbers and proportions were reported as appropriate. Proportions were based on the number of subjects with the outcome of interest over the total study population.

Ethics approval for the study was provided by the Queen's University Research Ethics Board.

## RESULTS

Between July 2004 and June 2005, a total of 127 surgical procedures were performed in 124 women. Phenazopyridine administration was confirmed in the medical chart, by the presence of either written orders, dictated notes stating that phenazopyridine was used, or nurses' notes documenting administration, in only 32 cases (Figure). Hospital charts were unavailable for review in three patients. These 32 patients made up our study population (Table 1). The procedures included both pelvic reconstructive and anti-incontinence procedures. Three women had surgery more than once during the period of the study, and each procedure was included as a separate event. Many subjects underwent multiple procedures in one surgery (Table 2).

Bilateral ureteric patency during intraoperative cystoscopy was confirmed in these 32 cases. Of note, the charts of all 124 patients were reviewed and all had documented ureteric patency intraoperatively, whether or not phenazopyridine use could be confirmed. The bladder mucosa was adequately inspected in all subjects; no inadvertent bladder injury or suture perforation was identified. Importantly, ureteric obstruction was not reported postoperatively in either the 32 cases retrospectively evaluated in this study, or

**Table 2. Index procedures of those who had intraoperative cystoscopies with phenazopyridine**

Procedures*	n
Pelvic reconstructive procedures	
Anterior colporrhaphy	3
Posterior colporrhaphy	4
McCall culdoplasty	4
Halban culdoplasty	5
Paravaginal repair	9
Abdominal sacrocolpopexy	2
Perineoplasty	1
Anti-incontinence procedures	
Burch colposuspension	9
TVT	18
Other procedures	
Hysterectomy	5
Subtotal abdominal hysterectomy	2
Vaginal hysterectomy	2
TVT mesh stretching	1

\*A given patient may have undergone more than one procedure

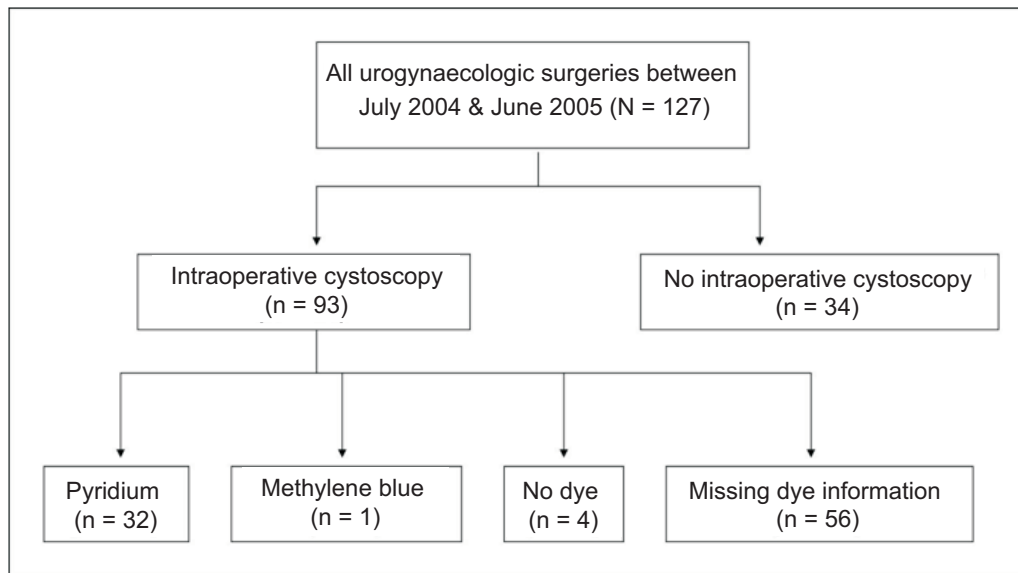
in any of the other patients in whom use of phenazopyridine could not be determined. On review of the anaesthesia records and hospital charts, there was no unexplained reaction or allergic reaction possibly related to phenazopyridine administration.

## DISCUSSION

In this series of 32 cases with confirmed phenazopyridine use, cystoscopic ureteric patency was confirmed intraoperatively and no ureteric injuries were missed, as shown by the lack of readmission or investigation for such complication. It is important to note that there are only two hospitals in the city in which the study took place, and they are linked by common medical records. We acknowledge that, given the incidence of ureteric injury following urogynaecological reconstructive surgery of 5% to 10%, a greater number of subjects would have been necessary to determine whether phenazopyridine was accurate in not missing ureteric injury, but efflux of phenazopyridine-stained urine was visible in all cases, which we believe was a more clinically relevant outcome. The bladder mucosa was visualized sufficiently to enable assessment for inadvertent injury or suture perforation and did not retain staining, which hypothetically could hinder detection of mucosal anomaly.

Moreover, ureteric patency could be confirmed rapidly by the evident orange-coloured jets of urine. Urine not

## Study group flow chart



containing dye may be distinguished from the fluid used to distend the bladder by its different tint, and ureteric efflux may be visible from the turbulence it creates, but this may be difficult to see even with an experienced eye. We do not know if surgical time was shortened by the use of phenazopyridine, but this was not a goal of the study.

In our study, we continued to see stained urine efflux from the ureters in cases lasting up to six hours. Very little is known about phenazopyridine pharmacokinetics, but recently Shang et al.<sup>15</sup> determined, using healthy fasting human volunteers, that phenazopyridine followed a two-site absorption model (stomach and intestine), with the first site showing absorption within 15 minutes and the second at two hours. Peak plasma concentration is obtained three hours after ingestion. Phenazopyridine's half-life is estimated at 75 minutes for the 100 mg oral dose and 48 minutes for the 200 mg dose. In another study, 43% of a single 200 mg oral dose of phenazopyridine was excreted in the 0–4 hour urine collection, and 60% was excreted in the first eight hours after administration.<sup>16</sup> This supports our observation of orange-stained urine even after prolonged cases. The impact of hydration and renal function on pharmacokinetics is unknown.

We did not collect data on renal function preoperatively and this may have been important. However, the few reports of complications in patients with impaired baseline renal function involved a greater duration of treatment with phenazopyridine than recommended<sup>13</sup> or higher doses administered.<sup>17</sup> It is thus unlikely that a single dose in a patient with impaired renal function and with no recent use of phenazopyridine would have a significant effect.

In fact, because phenazopyridine use was so rapidly seen to be simple and effective in our centre, its use in the setting of a planned intraoperative cystoscopy has continued despite the resumed availability of indigo carmine.

Not only is phenazopyridine effective and safe, but it is also inexpensive. One ampoule of indigo carmine costs \$34.50, but one tablet of phenazopyridine costs \$0.29. In this time of limited health care resources, such cumulative cost savings are potentially significant.

Indigo carmine remains the agent of choice if the decision to confirm ureteric patency is made intra-operatively. However, when a cystoscopy is planned a priori to confirm ureteric patency, phenazopyridine is safe, inexpensive and easy to administer immediately prior to surgery, making it an ideal dye agent for use in conjunction with intraoperative cystoscopy.

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