

Propofol-Associated Urine Discoloration: Systematic Literature Review

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Keywords

Propofol · Urine · Discoloration · Acute kidney injury · Anesthesia

Abstract

Introduction: Propofol occasionally induces a green or pink-cloudy urine discoloration. A lesser-known effect is green discoloration of hair, milk, liver, or stool. We aimed to gain insight into the features of these disturbances. **Methods:** The terms (“propofol” OR “fospropofol”) AND (“green” OR “pink” OR “cloudy” OR “pink-cloudy”) were searched in Excerpta Medica, MEDLINE/PubMed®, and Web of Sciences databases, with no language limit, from inception up to February 2023 (CRD4202236804). Articles reporting individually documented cases were retained, and data were extracted using a checklist. **Results:** Seventy-seven original reports documented 95 cases (including 13 subjects ≤18 years of age). Completeness of reporting was satisfactory in 33, good in 35, and excellent in 27 cases. Propofol-associated green urine discoloration was observed in 54 patients. In most instances ($n = 21$, 39%), propofol was given for ≥ 24 h. Sometimes, however, the urine discoloration developed after propofol for ≤ 3 h ($n = 12$, 22%). Propofol-associated urine discoloration was usually observed during the administration of this agent, but it was at times ($n = 11$) first recognized ≥ 3 h after propofol discontinuation. The duration of green urine discoloration was usually ≤ 24 h after stopping propofol. Propofol-associated green urine discoloration was never associated with worsening kidney function. A pink-cloudy urine discoloration was observed in 32 subjects with an acidic urine pH and increased uric acid excretion given propofol for ≤ 24 h. A stage I acute kidney injury was observed in 2 cases (6.3%) of propofol-associated pink-cloudy urine discoloration. Nine cases of non-urinary green discoloration were observed: hair ($n = 4$), breast milk ($n = 1$), liver ($n = 1$), stool ($n = 1$). **Conclusion:** Propofol is sometimes associated with a green (benign) or pink-cloudy (occasionally associated with mild acute kidney injury) urine discoloration. Rarely, non-urinary green discoloration has been reported.

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Published by S. Karger AG, Basel

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Introduction

The intravenous phenol anesthetic agent propofol is very commonly used because of its rapid effect, short action, and relatively safe profile [1]. Induction and maintenance of general anesthesia as well as sedation during non-surgical interventions and critical care both in children and adults are the main indications.

Some case reports indicate that propofol occasionally induces a pronounced green or pink-cloudy discoloration of the urine [2, 3]. A lesser-known effect is green discoloration of hair, milk, liver, or stool. Since case reports have limitations that hinder a scientific approach, we undertook a systematic review of the literature on these topics. The aims of this work were to gain insight into the features of these uncommon adverse drug reactions, characterize their time pattern, address the potential harm to the kidneys, and give suggestions for management.

Methods

Data Sources and Searches

This review was preregistered in the International Prospective Register of Systematic Reviews (CRD4202236804) and undertaken in agreement with the 2020 edition of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement, a set of items for reporting systematic reviews and meta-analyses [4]. We carried out a literature search in accordance with the Joanna-Briggs Institute Manual for Reviews [5] with no language and date limits using three databases: Excerpta Medica, MEDLINE/PubMed®, and Web of Science. The search terms were as follows: (“propofol” OR “fospropofol”) AND (“green” OR “pink” OR “cloudy” OR “pink-cloudy”). Articles listed in Google Scholar, articles already known to the authors, and references listed within bibliographies were also considered for inclusion. The first searches were conducted in December 2021. Notifications for new search results were inspected monthly until submission.

Study Selection and Data Extraction

Eligible were original articles and letters reporting individually documented humans given intravenous propofol presenting an otherwise unexplained green or pink-cloudy urine discoloration. Cases with green discoloration of hair, liver, milk, or stool were also considered.

In a first selection round, two authors independently screened the results of the initial literature search based on titles and abstracts. In a second round, they independently assessed the full-text articles of the remaining studies. For each round, discrepancies were solved by consensus and, if needed, by consultation with two senior authors.

In addition to demographics, from each reported case, we extracted following data: duration of the propofol administration; characteristics and duration of the discoloration; the termination of propofol after onset of discoloration; the existence of a time interval of 3 h or more between discontinuation of propofol and onset of urine discoloration; and laboratory data. The term “urine

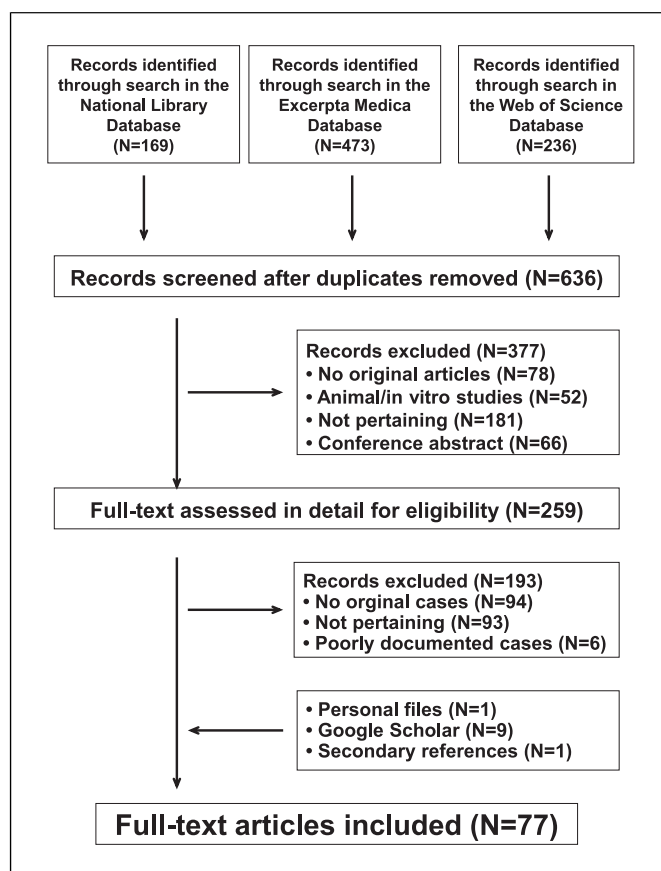


Fig. 1. Propofol and urine discoloration. Flowchart of the literature search process.

bag discoloration phenomenon” was used when urine of normal color became a different color in the urine bag [6].

Other causes of green urine color including the administration of further phenol groups containing drugs, methylene blue, pseudomonas urinary tract infections, or Hartnup disease were also considered [6, 7]. Pink-cloudy urine syndrome has been associated with excessive body weight [8]. For this analysis, the term excessive body weight was employed to denote subjects presenting with a body mass index of 25.0 kg/m² or more (or described in the article as overweight, adipose, or obese). Acute kidney injury was defined according to the KDIGO recommendations, which consider urine volume and creatinine [9]. One author entered the data into a pilot-tested spreadsheet, and the remaining author checked the entries.

Completeness of Reporting – Analysis

The completeness of each included case was graded as satisfactory, good, or excellent, as previously described [10, 11]. Basically, description completeness was evaluated according to following 5 components: (1) description of patient characteristics; (2) time pattern of propofol administration; (3) characteristics and duration of urine discoloration; (4) discontinuation and follow-up; and (5) laboratory characteristics. Each component was rated as 0, 1, or 2 and the reporting quality was graded according to the sum as satisfactory (<6), good (≥6), or excellent (>8).

Table 1. Characteristics of 95 patients with urinary or non-urinary green discoloration or pink-cloudy urine discoloration associated with the administration of propofol

	Green discoloration		Pink-cloudy urine discoloration	<i>p</i> value
	urinary	non-urinary		
Patients, <i>N</i>	54	9	32	
Female:male ratio	0.38	1.25	0.50	0.117
Age				
Years	50 [30–65]	37 [25–46]	27 [21–52]	0.1985
≤18 years, <i>N</i> (%)	7 (13)	1 (11)	5 (16)	0.7354

Data are presented as frequency (with percentage) or as median and interquartile range.

Pairwise deletion was used to deal with missing data. Categorical variables are presented as counts and were analyzed using the Fisher's exact test. Continuous variables are depicted as medians and interquartile ranges and were compared using the Kruskal-Wallis test with the post hoc Dunn-Bonferroni procedure. Statistical significance was defined by two-sided *p* values of <0.05.

As a final step, a consensus development conference among authors was held to summarize and compare green versus pink-cloudy urine discoloration regarding its frequency, time pattern, risk of acute kidney injury, and management. The frequency or probability was graded on a six-point Likert scale (never, very rarely, rarely, occasionally, very frequently, always).

Results

Search Outputs – Completeness of Reporting

The study flowchart is presented in Figure 1. For the final analysis, we retained 77 original reports [2, 3, 12–86] published since 1987: 30 from Asia, 27 from Europe, 17 from America, two from Oceania and one from Africa. Sixty-seven articles were published in English, six in Spanish, two in Dutch, one in Korean, and one in Turkish. The mentioned publications documented 95 cases of propofol-associated discoloration (and no case of fospropofol-associated discoloration): 54 (57%) with a green urine discoloration [2, 12–59], 32 (34%) with a pink-cloudy urine discoloration [3, 60–78], and nine (9.5%) with a non-urinary green discoloration [46, 79–86]. Completeness of reporting was satisfactory in 33 (35%), good in 35 (37%), and excellent in 27 (28%) cases.

Patients Characteristics

The 95 patients were 1.2–83 (median of 39) years of age, with a female:male ratio of 0.50. Patients with green urine discoloration, pink-cloudy urine discoloration, and non-urinary discoloration did not significantly differ with respect to age and sex (Table 1).

Urine Discoloration

Green Urine Discoloration

A green urine discoloration [2, 12–59] was observed in 53 and a urine bag green discoloration [34] in 1 case. The duration of propofol administration before discoloration of urine ranged between ≤3 and ≥72 h (Table 2). Propofol-associated urine discoloration was usually observed during the administration of this agent or immediately thereafter. In 11 cases, the urine discoloration was recognized ≥3 h after discontinuing propofol. In most cases, the duration of urine discoloration was ≤24 h after stopping propofol.

The administration of propofol was stopped after onset of urinary green discoloration in 23 but was continued in 9 cases (this information was not available for the remaining cases). In a Marfan patient, no urine green discoloration was noticed after propofol for 6 h. However, some days later, after receiving propofol during 4 h for a second surgical procedure, a green urine discoloration was observed [43]. Of note, in a Korean man given propofol for approximately 100 h, the intensity of urine discoloration was dependent on the propofol infusion rate [26]. The green urine discoloration observed after the administration of propofol was never associated with worsening kidney function (Table 2).

Pink-Cloudy Urine Discoloration

A pink-cloudy urine discoloration was reported in 32 cases with a median age of 27 years [3, 60–78]. An excessive body weight, an acidic urine pH, and increased uric acid excretion were documented in many cases (Table 3). Propofol-associated pink-cloudy urine discoloration occurred in patients given propofol for 24 h or less. The administration of propofol was stopped in all cases. Furthermore, parenteral fluid hydration was applied in many cases (*N* = 12). In most cases, the duration of pink-cloudy urine discoloration was 3 h or less after stopping propofol. A stage I acute kidney injury was observed in 2 cases [68, 74].

Table 2. Characteristics of 54 patients with green urine discoloration associated with the administration of propofol

	All	Without latency	With latency	Latency unknown	<i>p</i> value
Patients, <i>N</i>	54	33	11*	10	
Age					
Years	50 [30–65]	45 [28–66]	52 [30–59]	48 [33–64]	0.7814
≤18 years	7	6	0	1	0.312
Concurrent causes of green discoloration, <i>N</i>	2	0	2 ^a	0	
Duration of propofol administration before discoloration, <i>N</i>					0.0071
<0.5 h	6	3	2	1	
0.5–3 h	7	3	4	0	
4–24 h	9	6	3	0	
25–71 h	12	11	0	1	
≥72 h	9	9	0	0	
Information not available	11	1	2	8	
Urine bag discoloration syndrome	1	1	0	0	
Duration of discoloration after discontinuing propofol, ^b <i>N</i>					0.7277
≤3 h	7	6	1	0	
4–24 h	13	11	1	1	
25–71 h	11	4	4	3	
≥72 h	4	3	1	0	
Information not available	19	9	4	6	
Acute kidney injury, <i>N</i>	0	0	0	0	

Data are presented as frequency (with percentage) or as median and interquartile range. *3–6 h, *N* = 6; ≥7 h, *N* = 5. ^aMethylene blue [17], *N* = 1; methylene blue and metoclopramide [18], *N* = 1. ^bThe administration of propofol was continued for ≤2 h (*N* = 2), 24–64 h (*N* = 6), and approximately 300 h (*N* = 1) in 9 cases [2, 13, 19, 25, 26, 29, 30, 40, 44]. The tenth case is presented in the body of the manuscript [29].

Non-Urinary Green Discoloration

A non-urinary green discoloration was observed in 9 subjects, 1.8–60 (median 37) years of age: green hair [49, 79, 83, 85] in four, green breast milk in three [82, 84, 85], and green liver [80] or stool [81] in each 1 case. A green urine discoloration preceded the non-urinary discoloration in only 1 case [49]. The duration of propofol administration was less than 5 min in one, 90 min in one, and 7 days in a further case (this information was not available for the remaining cases).

Reasoned Summary of the Results

Relative frequency, time pattern, possible harms for kidney function, management, and risk factors of green or pink-cloudy urine discoloration induced by propofol are summarized in Table 4.

Discussion

The normal urine color results from the pigment urochrome and varies from light yellow to deep amber or dark yellow [6, 7]. An abnormal urine discoloration can

be alarming to both patients and healthcare professionals [6, 7]. The present systematic literature review delivers three main results. First, green urine discoloration mostly develops upon propofol administration for ≥24 h, rapidly subsides after discontinuation, and has never been associated with kidney injury. Second, pink-cloudy urine discoloration typically ensues with propofol administration for ≤24 h and is rarely associated with a mild acute kidney injury. Third, non-urinary green discoloration has rarely been reported.

Propofol-associated green urine discoloration, first observed in 1987 [1], results from a non-toxic phenolic chromophore, which is conjugated in the liver and eliminated in the urine [1]. Other medicines that contain phenol groups have been associated with green urine, including amitriptyline, flupirtine, flutamide, indomethacin, metoclopramide, mitoxantrone, promethazine, thymol, and the parenteral formulation of cimetidine [7]. Methylene blue is a further cause of green urine [7]. Blue urine is uncommon with methylene blue because it combines with urochrome to create a green color [7]. Finally, Hartnup disease and urinary tract infections caused by *Pseudomonas* species [7] and some traditional Persian medicines [87] have

Table 3. Characteristics of 32 patients with pink or cloudy urine discoloration associated with the administration of propofol

Age, years	27 [21–52]
Urine color, <i>N</i>	
Pink	23
Cloudy	9
Excessive body weight, <i>N</i>	9
Urine pH ≤ 6.0 , <i>N</i>	10
Increased uric acid excretion, <i>N</i>	13
Duration of propofol administration, <i>N</i>	
≤ 3 h	4
4–24 h	4
≥ 25 h	0
Information not given	24
Duration of urinary discoloration, <i>N</i>	
≤ 3 h	13
4–24 h	3
≥ 25 h	0
Information not given	16
Onset of discoloration ≥ 3 h after discontinuing propofol, <i>N</i>	2
Stage I acute kidney injury, <i>N</i>	2

Data are presented as frequency (with percentage) or as median and interquartile range.

Table 4. Relative frequency, time pattern, possible harms to kidney function, management, and risk factors of green or pink-cloudy urine discoloration induced by propofol

	Urine discoloration	
	green	pink-cloudy
Relative frequency	Occasionally	Rarely
Time pattern		
Duration of administration		
≤ 3 h	Occasionally	Very frequently
4–24 h	Occasionally	Very frequently
≥ 25 h	Very frequently	Never
Time interval ^a		
Without latency	Very frequently	Very frequently
With latency	Rarely	Very rarely
Discoloration ^b for ≤ 24 h	Very frequently	Very frequently
Excessive body weight*	Never	Occasionally
Acute kidney injury	Never	Rarely
Management	Unnecessary	Recommended

Following six-point Likert scale was used: always, very frequently, occasionally, rarely, very rarely, never. ^aOnset of discoloration ≥ 3 h after discontinuing propofol. ^bAfter discontinuing propofol. *Risk factor.

also been linked with this phenomenon. This review indicates that the green urine discoloration induced by propofol may occur from a few hours to a few days after its administration. The results also point out that the urine discoloration sometimes occurs more than 3 h after propofol is withheld and may persist for a few days after discontinuing it. Finally, the results indicate that there is no harm for the kidneys.

Generally, the association between propofol and pink-cloudy urine discoloration is less recognized than that with green discoloration. Pink urine syndrome, also termed brick dust urine (or sedimentum lateritium), refers to pink urine or pink urine sediment that occurs in the presence of precipitated uric acid [8, 74, 88, 89]. The pink hue results from the attachment of uricine, a pigment originated from bilirubin, to uric acid at an acidic

urine pH. Following four factors predispose to this syndrome: hyperuricemia (for great amounts of uric acid to appear in the urine, a large pool is required to draw from); an elevated fractional excretion of uric acid; acidic urine (a sine qua non for precipitation of uric acid); and an increased uric acid production (usually induced by conditions such as excessive body weight, fever, infections, stress, starvation, and acidosis). Pink urine syndrome is well recognized among apparently healthy newborn babies [8, 88] and in obese patients after surgery [8, 89]. The results of the present analysis demonstrate that propofol may predispose to pink urine syndrome. This likely arises from the fact that propofol increases uric acid excretion and activates uric acid synthesis [1, 74]. Considering that acute kidney injury is a possible consequence of propofol-associated pink urine syndrome, discontinuation of this hypnotic, fluid loading to increase urine output, and urinary alkalinization to convert uric acid to the more soluble urate salt deserve consideration in these cases.

Interestingly, this review demonstrates that propofol may also result in green hair, breast milk, liver, or stool. Fospropofol is a water-soluble propofol prodrug designed to overcome the disadvantages caused by the lipid-based formulation of propofol. No cases of fospropofol-associated urine discoloration have so far been reported. Nonetheless, this effect is expected given the need for the prodrug to convert to propofol [90].

The principal limitation of this review arises from the small number of published cases and the inherent risk of publication bias. Moreover, our analysis does not allow the establishment of the prevalence of urine discoloration caused by propofol. Furthermore, completeness of reporting cases was variable. Consequently, unfortunately, we were not able to provide data on underlying diagnosis, performed procedures, liver and kidney functions, or co-administered drugs. Finally, the suggested therapeutic approach is derived from pathophysiological considerations. In addition to the comprehensive literature search, which included three databases, this analysis has the strength of describing the time pattern of propofol-induced urine discoloration. Further, besides the rather known urine green tint, it also describes a pink-cloudy urine stain and the green discoloration of hair, liver, milk, or stool. This review analyzes the available information on the association between propofol and the occurrence of a pink-cloudy and green urine discoloration (Table 4).

In conclusion, green urine discoloration mostly develops upon propofol administration for ≥ 24 h, rapidly

subsides after discontinuation, and has never been associated with kidney damage. Pink-cloudy urine discoloration typically ensues with propofol administration for ≤ 24 h and has rarely been associated with a mild acute kidney injury. Non-urinary green discoloration has rarely been reported.

Statement of Ethics

An ethics statement is not applicable because this study is based exclusively on published literature.

Conflict of Interest Statement

Sebastiano A.G. Lava is the current recipient of research grants from Fonds de perfectionnement, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland; Fondation SICPA, Prilly, Switzerland; Fondazione Dr. Ettore Balli, Bellinzona, Switzerland; Fondazione per il bambino malato della Svizzera italiana, Bellinzona, Switzerland; and Frieda Locher-Hofmann Stiftung, Zürich, Switzerland.

Funding Sources

The study was partially supported by the Italian Ministry of Health (Ricerca Corrente 2021).

Author Contributions

Dr. Mario G. Bianchetti and Dr. Sebastiano A.G. Lava conceived the study design. Dr. Ana Lasica, Dr. Pietro Camozzi, and Dr. Mario G. Bianchetti wrote the draft of the manuscript. Dr. Ana Lasica, Dr. Cinzia Cortesi, and Dr. Mario G. Bianchetti conducted the literature search and performed article selection, data extraction and analysis, and reporting quality. Dr. Pietro Camozzi, Dr. Gregorio P. Milani, and Dr. Sebastiano A.G. Lava supervised data analysis. Dr. Federica M. Schera, Dr. Gregorio P. Milani, and Dr. Sebastiano A.G. Lava corrected the draft of the manuscript. All authors contributed to revising the manuscript and approved the final version.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its references. Further inquiries can be directed to the corresponding author.

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