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Study concept and design: Wong, Motulsky, Tamblyn.

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1. National Center for Health Statistics. Health, United States, 2010 with special feature on death and dying. <http://www.cdc.gov/nchs/data/abus/abus10.pdf>. Accessed July 23, 2015.

2. Gardarsdottir H, Heerdink ER, van Dijk L, Egberts ACG. Indications for antidepressant drug prescribing in general practice in the Netherlands. *J Affect Disord*. 2007;98(1-2):109-115.

3. Tamblyn R, Huang A, Kawasumi Y, et al. The development and evaluation of an integrated electronic prescribing and drug management system for primary care. *J Am Med Inform Assoc*. 2006;13(2):148-159.

4. Bartlett G, Tamblyn R, Kawasumi Y, Poissant L, Taylor L. Nonparticipation bias in health services research using data from an integrated electronic prescribing project: the role of informed consent. *Acta Bioeth*. 2005;11(2):145-159. <http://www.scielo.org/pdf/abioeth/v11n2/art05.pdf>.

5. Egale T, Winslade N, Hanley JA, Buckeridge DL, Tamblyn R. Enhancing pharmacosurveillance with systematic collection of treatment indication in electronic prescribing: a validation study in Canada. *Drug Saf*. 2010;33(7):559-567.

6. Carey V, Zeger SL, Diggle P. Modelling multivariate binary data with alternating logistic regressions. *Biometrika*. 1993;80(3):517-526. doi:10.2307/2337173.

COMMENT & RESPONSE

Risk of Anaphylaxis With Intravenous Iron Products

To the Editor The study by Dr Wang and colleagues¹ reported the risk of anaphylaxis with different intravenous iron products. I have several concerns.

One concern is the definition of *anaphylaxis*. In the article's online Supplement, both anaphylaxis criteria B and C include "injection of diphenhydramine." Given that diphenhydramine often is given both as a premedication (without evidence to support its use) and for treatment of minor reactions (flushing, myalgias of the chest and back, or headache), including it in the definition has the potential to greatly overestimate anaphylaxis rates. Diphenhydramine itself has been reported to cause somnolence, tachycardia, and hypotension.² Published data suggest that when diphenhydramine is used as premedication prior to intravenous iron, a significant majority of the reactions ostensibly attributed to the iron were due to diphenhydramine.³ In the Methods section, the authors noted that minor self-limited reactions such as minor allergic reactions would be wrongly labeled as anaphylaxis events. It would be informative to know the rates of anaphylactic reactions when patients who received diphenhydramine were excluded.

A second concern is that these data need to be put into perspective by comparing intravenous iron products with other commonly used drugs. For example, anaphylaxis to penicillin is reported in 10 to 50 per 100 000 treatment courses with a fatality rate of 1 to 2 per 100 000 courses, which is in the same range as that reported for intravenous iron.⁴

Third, death rates, which were reported in the article's online Supplement, were not discussed in the article. Reviewing data from eTables 3 and 4, it appears that death rates for all iron products were very similar, suggesting that safety rates are likely to be similar for all products and that the anaphylaxis rates for iron dextran may have been overestimated. Is it possible that criteria by which anaphylaxis was defined differed for different products?

Finally, it should be emphasized that the study population, with an average age of 73 to 74 years, was not representative of many patients receiving intravenous iron, including patients who have inflammatory bowel disease or heavy uterine bleeding, are pregnant, or are undergoing bariatric surgery. It is important not to extrapolate rates from older adults to these younger (and potentially healthier) individuals.

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1. Wang C, Graham DJ, Kane RC, et al. Comparative risk of anaphylactic reactions associated with intravenous iron products. *JAMA*. 2015;314(19):2062-2068.

2. Agostini JV, Leo-Summers LS, Inouye SK. Cognitive and other adverse effects of diphenhydramine use in hospitalized older patients. *Arch Intern Med*. 2001;161(17):2091-2097.

3. Barton JC, Barton EH, Bertoli LF, Gothard CH, Sherrer JS. Intravenous iron dextran therapy in patients with iron deficiency and normal renal function who failed to respond to or did not tolerate oral iron supplementation. *Am J Med*. 2000;109(1):27-32.

4. Lieberman P, Camargo CA Jr, Bohlke K, et al. Epidemiology of anaphylaxis: findings of the American College of Allergy, Asthma and Immunology Epidemiology of Anaphylaxis Working Group. *Ann Allergy Asthma Immunol*. 2006;97(5):596-602.

In Reply In response to Dr DeLoughery's concern about diphenhydramine, provided is a sensitivity analysis that excluded all anaphylaxis cases with the claim of "injection of diphenhydramine" (Table 1). Results are consistent with the primary analysis.

Regarding incidence rates, as discussed in our article, rates from our study were substantially lower than those reported from clinical trials of intravenous iron products. Although other study populations might have contributed to the observed differences, other differences in identifying and reporting anaphylaxis cases during clinical trials and during general clinical practice might also be relevant. Practicing physicians might not classify less severe or atypical anaphy-

Table 1. Risk of Anaphylaxis Without Diphenhydramine at First Administration for New Intravenous Iron Product Users

Intravenous Iron	Iron Sucrose	Ferumoxytol	Iron Dextran	Iron Gluconate
2003-2013				
No. of anaphylaxis cases	26		91	21
No. of new users	264 166		247 500	94 400
Rate per 100 000 persons (95% CI)	9.8 (6.6-14.6)		36.8 (29.8-45.4)	22.2 (14.1-34.6)
Adjusted OR (95% CI) ^a	1 [Reference]		3.6 (2.2-6.0)	2.2 (1.2-4.2)
P value ^b			<.001	.01
2010 to 2013				
No. of anaphylaxis cases	12	17	34	9
No. of new users	134 836	82 117	77 935	34 029
Rate per 100 000 persons (95% CI)	8.9 (4.8-16.0)	20.7 (12.5-33.9)	43.6 (30.7-61.7)	26.4 (12.9-52.2)
Adjusted OR (95% CI) ^a	1 [Reference]	2.4 (1.0-5.7)	4.8 (2.2-10.8)	2.9 (1.0-8.3)
P value ^b		.06	<.001	.04

Abbreviation: OR, odds ratio.

^a Adjusted for age, indication, coronary heart disease, and hypertension.

^b P value adjusted for multiple comparisons.

Table 2. Death Rates on Day of Incident Intravenous Iron Administration in the Nondialysis Population

Intravenous Iron	No. of Deaths	No. of New Users	Death Rate per 100 000 Persons (95% CI)
2003-2013			
Iron			
Dextran	10	247 500	4.0 (1.9-7.4)
Gluconate	11	94 400	11.7 (5.8-20.8)
Sucrose	19	264 166	7.2 (4.3-11.2)
2010-2013			
Iron			
Dextran	3	77 935	3.8 (0.8-11.2)
Gluconate	2	34 029	5.9 (0.7-21.2)
Sucrose	12	134 836	8.9 (4.6-15.5)
Ferumoxytol	6	82 117	7.3 (2.7-15.9)

lactic cases as anaphylaxis; thus, the sensitivity of the anaphylaxis algorithm used in our study was probably low. We do not recommend comparing the crude incidence rates of anaphylaxis from this study with rates of other medications, especially if the latter estimates were based on different data sources or study methods.

Also provided are all-cause mortality by treatment groups, which show the number of deaths that occurred on the same day as an intravenous iron administration (Table 2). Only a few deaths were identified in the study population. In addition, iron dextran is the only product that has a broad indication for iron deficiency anemia, whereas other nondextran products are restricted to patients with iron deficiency anemia and chronic kidney disease. Patients who received iron dextran were generally healthier than patients who received nondextran iron products, with fewer patients having chronic kidney disease and other chronic diseases, which may explain the low mortality rate in the iron dextran group. Therefore, we do not think the risk of anaphylaxis in the iron dextran group was overestimated. An adjusted analysis is not feasible due to the low incidence

of death. Interestingly, out of 444 patients identified with anaphylaxis in the study, 5 of them died within 2 days of anaphylaxis diagnosis (2 in iron dextran group, 1 in iron gluconate group, and 2 in ferumoxytol group).

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Intended vs Reported Scope of Practice

To the Editor The article by Dr Coutinho and colleagues¹ found that graduating family medicine residents reported inten-