The *primum non nocere* principle

More than ever, *primum non nocere* (first, do no harm) is the main thought we all should have in our minds at this particular moment of the human being!

Jean Guillaume Auguste Lugol, the famous French physician who developed the "5% potassium iodide solution" (called Iodine) would never anticipate the importance of his once-known therapeutic substance when presenting his *Mémoire sur l'émploi de l'iode dans les maladies scrofuleuses* in 1829 at the Royal Academy of Sciences of Paris.[1] Although Professor Lugol's original efforts to use iodine to stop the progress of tuberculosis proved to be unsuccessful in the following years, it was Walter Schiller's pioneer studies of early cervical cancer histogenesis,[2-4] after nearly 100 years, that built up a "noble" place for this solution among the medical diagnostic resources that were to come, especially for upper GI endoscopy.

Back to chemistry lessons: Lugol's solution contains potassium iodide (KI) and a stoichiometric amount of elemental free iodine (I_2), which confers to it varying strengths, the most commonly available from 1% to 5%. By reacting with the I_2, iodine ion (I^-) forms a triiodide ion (I_3^-), which is soluble in water and has its presence revealed by a yellow or brown color according to its low or high concentration in the solution, respectively.[5] Having the essential capability of reacting with glucose chains, a significant amounts of I_3^- is "ready to work" wherever the glucose chains are stored.

In contrast to malignant nonkeratinized epithelial cells, the typical cells contain abundant glycogen, a polymeric biomolecule composed of thousands of linear chains of 8 to 12 glucose units, on average.[6] After Lugol's solution is sprayed onto stratified squamous epithelium, the intracellular glucose chains coil up, fitting inside the I_3^-. This reaction soon turns into an absorbing deep dark brown light one, mimicking the "iodine clock reaction" phenomenon and indicating silently (and for a short time) the presence of a well-glycogenated normal epithelium: the longer the glucose chains are, the more intense the color reaction will be.[7]

Evaluating a variety of patients with an insightful eye, Professor Walter Schiller registered areas of different shades of brown staining on cervical mucosa. Interpreted as Lugol positive, or Schiller negative, or simply, iodine represented either benign conditions (eg, columnar epithelium, atrophic squamous epithelium, ulcers, infection, hyperkeratosis, or traumatic desquamation) or the more relevant suggestive premalignant (eg, metaplastic epithelium, dysplastic epithelium) and malignant conditions. Although not pathognomonic, his work drove the attention of the scientific community to learn the boundaries of high energy-consuming epithelial lesions. "Pathologic epithelium, especially carcinomatous, does not take up the stain, but instead remains light, or at most slightly yellowish." His words, published in 1933, remain effective today.[8]

Harmful relationships connecting silent (often asymptomatic) superficial lesions to subtle changes in the mucosa and high tumor aggressiveness (cancer rapidly invades through the wall) are among the reasons why ESCC is easily overlooked during endoscopic examination or is diagnosed late. Therefore, the detection of precursor lesions and/or ESCC at an earlier and potentially curable stage of the disease is critical (and desirable) to improve patient survival.

Being the seventh most common cancer in the world (3.2% of all cases) and consisting essentially of the esophageal squamous cell carcinoma (ESCC) histiotype, esophageal cancer remains in the sixth position in mortality (5.3%) according to GLOBOCAN 2018.[9] With a geographically uneven incidence (21-fold difference between the countries with the lowest and the highest incidence rates), a high lethality (89%), and a predominantly advanced staging at diagnosis, ESCC bears the burden of a poor overall 5-year survival rate (16.9%).[10] Harmful relationships connecting silent (often asymptomatic) superficial lesions to subtle changes in the mucosa and high tumor aggressiveness (cancer rapidly invades through the wall) are among the reasons why ESCC is easily overlooked during endoscopic examination or diagnosed late. Therefore, the detection of precursor lesions and/or ESCC at an earlier and potentially curable

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The development of a flexible fiberoptic endoscope by Hirschowitz et al[11] dramatically changed endoscopic practice in the late 1950s and allowed further conformable and direct inspection of the upper GI lumen. Soon, in 1966, Voegeli[12] kicked off the era of enhanced imaging for endoscopic esophageal investigation by reporting the first use of Lugol's solution on nonkeratinized epithelial mucosa. Subsequent findings by Rywlin and Ortega[13] in 1970 (glycogenic acanthosis), Brodmerkel[3] in 1971 (diagnosis of esophageal diseases), Nothmann et al[14] in 1972 (characterization of squamocolumnar junction limits), and Toriie et al[15] in 1975 (diagnosis of esophageal diseases), to mention some workers, helped promote the use of vital chromoendoscopy in the differential diagnosis of esophageal diseases. As an example, some of the terms established by them (eg, glycogenic acanthosis) are still in use today.

As a well-established concern, improved endoscopic detection and delineation of the limits of high-grade dysplasia and/or early cancerous lesions in the high-risk cancer population (eg, tobacco and alcohol users, patients with already diagnosed ESCC or head-and-neck carcinoma) should be pursued whenever optimal visualization of squamous mucosal abnormalities is required.[16,17] Widely (and also wisely) available today, Lugol's staining turned into an invaluable tool in characterizing the esophageal epithelial surface as a simple and quick technique of progressively spraying the solution on the surface to stain the mucosa with a brown pattern, except for atypical lesions.[15] For these lesions, the sensitivity for mild dysplasia, moderate dysplasia, severe dysplasia, and cancer was 45.9%, 55.3%, 87.0%, and 97.7%, respectively.[18] Given the fact that "hidden" esophagel cancer may continue evolving asymptomatically, especially in low-income populations, all efforts to prompting resection of these lesions or to better direct biopsies are worth it. That is one reason why the inexpensive Lugol's solution became so important to the endoscopy family.

On the other hand, despite the remarkable achievements and benefits of iodine staining in endoscopy, its routine use would not be without a "cost" to the patients, ie, without having adverse effects. Regardless of the concentration of the free corrosive iodine component in the solution, several studies mention mucosal irritation leading to acute and late adverse symptoms after Lugol's staining: retrosternal and/or epigastric pain, chest discomfort, acute esophageal and gastric injury (eg, chemical esophagitis, ulcer), and possible allergic reactions are among a broad collection of the reported reactions.[19-21] All these "friendly fire" clinical symptoms may further discourage the clinical use of the iodine substance and decrease early identification of premalignant and malignant lesions. Like a reentry mechanism, in the end, they may prevent early diagnosis of esophageal cancer.

It is already known that sodium thiosulfate solution (STS) eases the symptoms induced by mucosal staining with Lugol's solution. Therefore, it has been recommended for routine use after Lugol's staining.[22] However, not diffusely used, it has been suggested to neutralize just the iodine on the surface of the squamous epithelium.

At this point, would the use of the iodine solution to clarify our "endoscopic myopia" justify the risk of promoting patients' retrosternal pain and/or chest discomfort and leaving these symptoms unpunished? Or would it be possible to step outside the box, as Keith Ferrazzi suggests, and "act the way into a new way of thinking"? Is there any hidden solution waiting to be found?

The nonmaleficence precept, derived from the maxim *primum non nocere* (do no harm) principle, is one of the principal precepts of bioethics. It reminds healthcare personnel to (re)consider the possible harm that any intervention might do.

In this issue of *Gastrointestinal Endoscopy*, the study by Jin et al,[23] "The safety and efficacy of 2% vitamin C solution (VCS) spray for relief of mucosal irritation caused by Lugol chromoendoscopy: a multicenter, randomized, double-blind, parallel trial," may shed light on relieving the discomfort of symptoms from the topical application of Lugol's solution. Following an old statement that says "to have something new, somebody needs to do something never tried before," the authors tested spraying VCS on mucosal surface after iodine solution and proved that it also neutralizes free iodine, relieving the subsequent adverse symptoms.

Commended on having first tested the effect of different concentrations of vitamin C both in vitro and ex vivo (experiments on pig esophageal specimens), the authors observed that a 2% VCS had an optimal discoloration effect on the esophageal brown iodine-stained mucosa without histologic damage.[23] Only then did they translate the results of these bench studies into a noninferiority randomized translational trial. Washing the esophageal mucosa of patients undergoing Lugol chromoendoscopy (10 mL 2% Lugol iodine solution) with a different solution, and evaluating patients' descriptions of their clinical symptoms after 5 and 35 minutes of ending the examinations, they compared the improving symptoms in 3 distinct groups of 80 patients each, using in the normal saline (NS) group an NS solution (20 mL), in the STS group a 5% STS, and, finally, in the VCS group, a 2% VCS.[23]

With the reduction of acute and late adverse symptom severity scores as primary endpoints and the discoloration effect of esophageal brown iodine-stained mucosa as a secondary endpoint, they found no difference between the STS and VCS groups regarding the reduction of both acute and late adverse symptom scores except when they were determined against NS, where both were superior.[23]

Interestingly, the authors also found that VCS better alleviated acute acid regurgitation and late retrosternal discomfort or pain when compared with STS. VCS and STS quickly discolored the iodine-stained mucosa in a similar way, performing better than NS.[23]

Despite the encouraging results obtained with VCS, one must remember that this trial was designed as a noninferiority comparison, ie, the study aimed to demonstrate that an experimental treatment is not substantially worse than a control treatment (placebo or active control). Noninferiority trials may be performed in situations where conducting a placebo control trial is unethical.[22] Moreover, in favor of the authors' choice of protocol design, the noninferiority trials may also be used in the investigation of important advantages of the new treatment over the standard ones, especially in terms of improved safety, convenience, better compliance, or cost.

Currently considered the best experimental design to assess issues related to treatment and prevention, noninferiority trials have gained popularity within the past decades and are more complex to design, conduct, and interpret than conventional superiority trials. There are some complicated issues with trials of this type that make them less reliable than typical superiority trials.[24] Among others, noninferiority margin (the maximum acceptable extent of clinical noninferiority of an experimental treatment), assay sensitivity (the ability to distinguish effective treatments from those that are less effective or ineffective), and sample size are important factors to consider.[24]

As for the study by Jin et al,[23] the authors found that acid regurgitation/heartburn was experienced by 33% and 15% of the patients in the STS and VCS groups, respectively, generating statistical significance ($P = .017$).[23] Digging into this result, it should be interpreted with caution because it could be a false positive result, representing a complicated issue as mentioned above. Accordingly, in a superiority trial, a sample size of 120 patients in each group would be needed to detect this same difference (ie, 33% vs 15% in a dichotomous endpoint).

Therefore, the fair conclusion (along with the take-home message) is that VCS is noninferior compared with STS in preventing the adverse events related to Lugol spraying of the esophageal mucosa. On the basis of the results obtained by Jin et al[23] with the use of NS, it is also noteworthy that an "antidote" solution, either VCS or STS, should be used as an integral part of Lugol chromoendoscopy for the sake of our patients' comfort. Not less important, availability and costs will certainly influence the choice of VCS or STS solutions in the different endoscopy services worldwide.

Finally, keeping alive the principle of the *primum non nocere* in their research, we thank the authors for expanding our arsenal of drugs to mitigate patient discomfort caused by Lugol's chromoendoscopy.

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Simone Guaraldi, MD, MSc, PhD, SOBED, ASGE
Seção de Endoscopia
Instituto Nacional de Câncer
Programa de Carcinogênese Molecular
Instituto Nacional de Câncer
Rio de Janeiro
Fauze Maluf-Filho, MD, MSc, PhD, FASGE
Instituto do Câncer of São Paulo
Department of Gastroenterology
University of São Paulo
São Paulo, Brazil

Abbreviations: ESCC, esophageal squamous cell carcinoma histotype; I^-, iodine ion; I_2, elemental free iodine; I_3^-, triiodide ion; NS, normal saline solution; STS, sodium thiosulfate solution; VCS, vitamin C solution.

REFERENCES

1. Powell JL. Powell's pearls: Jean Guillaume Auguste Lugol, MD (1788-1851). Obstet Gynecol Surv 2006;61:1.
2. Powell JL. Biographic sketch: Powell's Pearls: Walter Schiller, MD (1887-1960). Obstet Gynecol Surv 2004;59:319-20.
3. Brodmerkel GJ Jr. Schiller's test: an aid in esophagostopic diagnosis. Gastroenterology 1971;60:813-8.
4. Schiller W. Early diagnosis of carcinoma of the cervix. Surg Gynecol Obstet 1933;56:210-2.
5. Iodine Test https://en.wikipedia.org/wiki/Iodine_test. Available at: https://en.wikipedia.org/w/index.php?title=Iodine_test&oldid=961160990. Accessed June 6, 2020.
6. Glycogen. 2020. Available at: https://en.wikipedia.org/wiki/Glycogen. Accessed June 7, 2020.
7. Cartwright H. Kinetics of the persulfate-iodide clock reaction 2006. Available at: http://cartwright.chem.ox.ac.uk/tlab/experiments/502.pdf. Accessed June 8, 2020.
8. Schiller, Walter (1887–1960): Schiller's Test. In: Baskett T. Eponyms and Names in Obstetrics and Gynaecology. Cambridge: Cambridge University Press; 2019. p. 372.
9. Cancer fact sheets - Oesophagel cancer Cancer Today - IARC: GLOBOCAN 2018; 2020. Available at: https://gco.iarc.fr/today/data/factsheets/cancers/6-Oesophagus-fact-sheet.pdf. Accessed June 8, 2020.
10. Zhang Y. Epidemiology of esophageal cancer. World J Gastroenterol 2013;19:5598-606.
11. Hirschowitz BI, Peters CW, Curtiss LE. Preliminary report on a long fiberscope for examination of stomach and duodenum. Med Bull (Ann Arbor) 1957;23:178-80.
12. Voegeli R. [Schiller's iodine test in the diagnosis of esophageal diseases. Preliminary report]. Pract Otorhinolaryngol (Basel) 1966;28:230-9.
13. Rywlin AM, Ortega R. Glycogenic acanthosis of the esophagus. Arch Pathol 1970;90:439-43.
14. Nothmann BJ, Wright JR, Schuster MM. In vivo vital staining as an aid to identification of esophagogastric mucosal junction in man. Am J Dig Dis 1972;17:919-24.
15. Toriie S, Akasaka Y, Yamaguchi K, et al. New trial for endoscopical observation of esophagus by dye spraying method. G E N 1976;30:159-65.

16. Dawsey SM, Fleischer DE, Wang GQ, et al. Mucosal iodine staining improves endoscopic visualization of squamous dysplasia and squamous cell carcinoma of the esophagus in Linxian, China. Cancer 1998;83:220-31.
17. Bugter O, van de Ven SEM, Hardillo JA, et al. Early detection of esophageal second primary tumors using Lugol chromoendoscopy in patients with head and neck cancer: a systematic review and meta-analysis. Head Neck 2019;41:1122-30.
18. Li J, Xu R, Liu M, et al. Lugol chromoendoscopy detects esophageal dysplasia with low levels of sensitivity in a high-risk region of China. Clin Gastroenterol Hepatol 2018;16:1585-92.
19. Gotoda T, Kanzaki H, Okamoto Y, et al. Tolerability and efficacy of the concentration of iodine solution during esophageal chromoendoscopy: a double-blind randomized controlled trial. Gastrointest Endosc 2020;91:763-70.
20. Park JM, Seok Lee I, Young Kang J, et al. Acute esophageal and gastric injury: complication of Lugol's solution. Scand J Gastroenterol 2007;42:135-7.
21. Thuler FP, de Paulo GA, Ferrari AP. Chemical esophagitis after chromoendoscopy with Lugol's solution for esophageal cancer: case report. Gastrointest Endosc 2004;59:925-6.
22. Kondo H, Fukuda H, Ono H, et al. Sodium thiosulfate solution spray for relief of irritation caused by Lugol's stain in chromoendoscopy. Gastrointest Endosc 2001;53:199-202.
23. Jin D, Wang J, Zhan Q, et al. The safety and efficacy of 2% vitamin C solution spray for relief of mucosal irritation caused by Lugol chromoendoscopy: a multicenter, randomized, double-blind, parallel trial. Gastrointest Endosc 2020;92:554-64.
24. Hahn S. Understanding noninferiority trials. Korean J Pediatr 2012;55:403-7.