EASL EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER | JOURNAL OF HEPATOLOGY

Vinyl chloride and the liver: Misrepresentation of epidemiological evidence

To the Editor:

In reviewing the epidemiological literature on vinyl chloride monomer (VCM) and hepatocellular carcinoma (HCC), Sherman incurred errors and misrepresentation of the overall evidence [1].

First, the author provides a surprising estimate of an annual incidence of liver angiosarcoma (LAS) among US exposed workers equal to 0.014/100,000. This is probably the incidence of LAS in the US general population which was about 0.014–0.025/100,000 in 1964–1974 [2]. Indeed, the mortality (close to incidence) rate was 15.2/100,000 (48 cases in 316,520 person-years) in the North American cohort of VCM workers [3], three orders of magnitude higher than that reported by Sherman.

Second, the author contradicts himself in regards to the association between VCM and HCC in the European cohort [4], affirming, on page 1077, that "this study did not suggest that there was a dose–response relationship between exposure and the development of HCC", and on page 1080 that "there seems to be a trend towards a higher HCC death rate with increasing dose".

Third, our case–control study [5] was presented as a "cohort study" on page 1078, while on page 1077 the study from Ward (cohort study) [4] and that from Boffetta (meta-analysis of cohort studies) [6] were confused with "case–control studies". In the same statement, Sherman affirms that "case–control studies" use "non-exposed workers as controls". This is similarly incorrect, since controls in a case–control study are subjects without disease and not without exposure.

Fourth, he reports that case–control studies used office workers as controls, with non-comparability with cases in regards to viral hepatitis and alcohol consumption. This is not true, as the only case–control study that he cites is our study [5], where cases and controls were all blue-collar workers coming from the same VCM plant.

Fifth, he claims that in our analyses when examining interactions, each cell contained 10 or fewer cases, making results unreliable even if statistically significant. Nonetheless, if the reader does not like the analysis of interactions, he can rely on the full analysis of thirteen cases of HCC and 40 cases of liver cirrhosis (LC), that were separately compared to 139 referents without chronic liver diseases or cancer in a case–control study nested in a cohort of 1658 VCM workers. By holding the confounding factors (alcohol, age, markers of B/C viruses) constant at logistic regression, each extra increase of 1000 ppm $\times$ years of VCM cumulative exposure was found to increase the risk of HCC by 71% (odds ratio, OR = 1.71; 95% confidence interval, CI = 1.28–2.44) and the risk of LC by 37% (OR = 1.37; CI = 1.13–1.69) [5].

Sixth, Sherman reports that results from our study are doubtful because cumulative exposure was associated with cirrhosis but is also a function of age. Indeed, our analyses were stratified for year of birth (controlling for age carried similar results). Furthermore, he states that the same objection applies to the study of Pirastu et al. [7]. This does not make sense, since this was a cohort study where the measure of association (standardized mortality ratio) takes into account age and calendar period.

Seventh, Sherman claims that an ascertainment bias could have affected the diagnosis of HCC in the epidemiological studies reviewed since they rely upon death certificates and not "upon autopsy data, biopsy data, angiography or a diagnostic elevated AFP" (alpha-fetoprotein, a serological marker of HCC, is rarely increased in LAS). In our study [5], however, out of 13 cases of HCC, eight were confirmed by histology and five based on the criteria – focal hepatic lesions at ultrasonography and alpha-fetoprotein greater than 400 μg/L – issued by the Italian Association Study of Liver and British Society of Gastroenterology [8].

The author declares in a footnote to be "consultant to the European Council of Vinyl Manufacturer's for the workshop on the relationship between VCM and HCC" [1]. Furthermore, in his conclusion Sherman cites as supporting evidence only two papers [9,10] – two reviews both written by consultants of the vinyl chloride industry in a lawsuit against the management of a VCM plant. We think that a conflict of interests does not represent a fatal flaw for research until it does not heavily affect the quality of papers. Moreover, in such a specific matter it is difficult not to have some conflict of interest: two authors (G.M. and D.M.) of the present letter were consultants of Public Prosecutors in the above lawsuit.

With his paper carrying errors and inconsistencies, Sherman concludes that the relation between VCM and HCC remains "unproven". This is a misrepresentation of the current epidemiological evidence that, according to the International Agency for Research on Cancer, there is "sufficient evidence" that exposure to vinyl chloride in humans causes both HCC and LAS [11].

Conflict of interests

Two of the authors (G.M. and D.M.) were consultants of Italian Government and Public Prosecutors in a lawsuit opposing workers, local municipalities, and the Italian Government against the management of an Italian vinyl chloride plant.

References

[1] Sherman M. Vinyl chloride and the liver. J Hepatol 2009;51:1074–1081.
[2] Falk H, Herbert J, Crowley S, Ishak KG, Thomas LB, Popper H, et al. Epidemiology of epatic angiosarcoma in the United States 1964–1974. Environ Health Perspect 1981;41:107–113.
[3] Mundt KA, Dell LD, Austin RP, Luippold RS, Noess R, Bieglow C. Historical cohort study of 10,109 men in the North American vinyl chloride industry, 1942–72: update of cancer mortality to 31 December 1995. Occup Environ Med 2000;57:774–781.

[4] Ward E, Boffetta P, Andersen A, Colin D, Comba P, Deddens JA, et al. Update of the follow-up of mortality and cancer incidence among European workers employed in the vinyl chloride industry. Epidemiology 2001;12:710–718.
[5] Mastrangelo G, Fedeli U, Fadda E, Valentini F, Agnesi R, Magarotto G, et al. Increased risk of hepatocellular carcinoma and liver cirrhosis in vinyl chloride workers: synergistic effect of occupational exposure with alcohol intake. Environ Health Perspect 2004;112:1188–1192.
[6] Boffetta P, Matisane L, Mundt KA, Dell LD. Meta-analysis of studies of occupational exposure to vinyl chloride in relation to cancer mortality. Scand J Work Environ Health 2003;29:220–229.
[7] Pirastu R, Baccini M, Biggeri A, Comba P. Epidemiologic study of workers exposed to vinyl chloride in Porto Marghera: mortality update. Epidemiol Prev 2003;27:161–172.
[8] Ryder SD. Guidelines for the diagnosis and treatment of hepatocellular carcinoma (HCC) in adults. Gut 2003;52 (Suppl. 3):1–8.
[9] Dragani TA, Zocchetti C. Occupational exposure to vinyl chloride and risk of hepatocellular carcinoma. Cancer Causes Control 2008;19:1193–1200.
[10] McLaughlin JK, Lipworth L. A critical review of the epidemiologic literature on health effects of occupational exposure to vinyl chloride. J Epidemiol Biostat 1999;4:253–275.
[11] Grosse Y, Baan R, Straif K, Secretan B, El Ghissassi F, Bouvard V, et al. Carcinogenicity of 1,3-butadiene, ethylene oxide, vinyl chloride, vinyl fluoride, and vinyl bromide. Lancet Oncol 2007;8:679–680.

Giuseppe Mastrangelo*
Department of Environmental Medicine and Public Health, University of Padova, Padova, Italy
* Corresponding author. Address: University of Padova, Via Giustiniani 2, 35128 Padova, Italy.
Tel.: +39 049 8212543; fax: +39 049 8212542.
E-mail address: giuseppe.mastrangelo@unipd.it

Diego Martines
Department of Surgical and Gastroenterological Sciences, University of Padova, Padova, Italy

Ugo Fedeli
SER-Epidemiological Department, Veneto Region, Castelfranco Veneto, Italy

Selective rather than routine approach to endosopic retrograde cholangio-pancreatography in diagnosis of biliary atresia

To the Editor:

Petersen and colleagues describe their experience in the "routine" use of endoscopic retrograde cholangio-pancreatography (ERCP) in children awaiting explorative laparotomy (EL) for suspected biliary atresia (BA) [1]. They report that almost 25% of the infants have avoided surgery after documenting a patent biliary tree. The quoted specificity of ERCP in diagnosing BA was 73% [1].

The aim of avoiding unnecessary surgery is valiant and undoubted, but we feel that a non-selective approach to a relatively invasive procedure in jaundiced infants, who may be recovering from the potentially recoverable liver injury, such as the one secondary to prematurity, total parenteral nutrition, severe haemolysis and/or infection, may not be justified. Repeated general anaesthetic, required by combined ERCP/EL, in a jaundiced child carries additional risks outside the usual economic arguments. Sixty (43%) infants referred to Petersen et al. who underwent ERCP actually did not have BA. Suspected BA may mean different things for different centres and submitting all referred children to ERCP may not be indicated, despite the technical excellence.

In this study the "pre-selection" information, including ultrasound findings or liver histology, was unfortunately not presented, although the authors have quoted experiences where specificity for percutaneous liver biopsy was 96% [2] and 89% [3], respectively. An early study from our centre found the liver histology as sufficient for diagnosis of BA in 86% infants with neonatal cholestasis [4]. Finally, in the study by Petersen et al. the children undergoing ERCP/EL combination were up to 174 days old, an age where benefits of corrective surgery are somewhat dubious.

We have recently reported our own tertiary centre experience on use of ERCP in 48 cholestatic infants younger than 100 days, representing only around 4% of infants with neonatal cholestasis, where diagnosis after comprehensive hepatological work-up remained unclear [5]. EL was avoided in 42% of children, while selective ERCP had a specificity of 87% for diagnosis of BA [5].

Protocols for investigating infants with prolonged neonatal cholestasis will continue to differ from centre to centre, but there is no substitute for evaluation of all the available clinical information, including monitoring stool colour and its change on choleretics [6]. ERCP is a very welcome addition to the diagnostic algorithm for the diagnosis of BA, but in our view should be used selectively once other, less invasive, tests have proven inconclusive.

References

[1] Petersen C, Meier PN, Schneider A, Turowski C, Pfister ED, Manns MP, et al. Endoscopic retrograde cholangiopancreaticography prior to explorative laparotomy avoids unnecessary surgery in patients suspected for biliary atresia. J Hepatol 2009;51:1055–1060.
[2] Park WH, Choi SO, Lee HJ, Kim SP, Zeon SK, Lee SL. A new diagnostic approach to biliary atresia with emphasis on the ultrasonographic triangular cord sign: comparison of ultrasonography, hepatobiliary scintigraphy, and liver needle biopsy in the evaluation of infantile cholestasis. J Pediatr Surg 1997;32:1555–1559.
[3] Esmaili J, Izadyar S, Karegar I, Gholamrezanezhad A. Biliary atresia in infants with prolonged cholestatic jaundice. diagnostic accuracy of hepatobiliary scintigraphy. Abdom Imaging 2007;32:243–247.
[4] Manolaki AG, Larcher VF, Mowat AP, Barrett JJ, Portmann B, Howard ER. The prelaparotomy diagnosis of extrahepatic biliary atresia. Arch Dis Child 1983;58:591–594.
[5] Shanmugam NP, Harrison PM, Devlin J, Peddu P, Knisely A, Davenport M, et al. Selective use of endoscopic retrograde cholangiopancreatography in the diagnosis of biliary atresia in infants younger than 100 days. J Pediatr Gastroenterol Nutr 2009;49:435–441.
[6] Hadzic N. Biliary atresia. In: Jara P, editor. Liver diseases in children. International hepatology updates. Barcelona: Permanyer Publications; 2009.

Nedim Hadzic,
Phillip M. Harrison
King's College Hospital, London, United Kingdom
E-mail address: nedim.hadzic@kcl.ac.uk