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Pharmaceutical Products Derived from Swine: Is There any Potential Risk of Hepatitis E Virus Transmission?

JR Mesquita[1,2], RMS Oliveira[3] and MSJ Nascimento[3]*

[1]Agrarian Superior School (ESAV), Polytechnic Institute of Viseu, Portugal

[2]Centre for Studies in Education, Technologies and Health (CI&DETS), Polytechnic Institute of Viseu, Portugal

[3]Department of Biological Sciences, University of Porto, Portugal

Abstract

Hepatitis E virus (HEV) has become a growing Public Health concern in the last decade in industrialized countries after the discovery of autochthonous cases of hepatitis. Infections are usually acquired from zoonotic transmission from pigs but other routes of transmission in industrialized countries have been described and others yet have been suspected. Iatrogenic transmission such as transfusion of HEV–contaminated blood products and transplantation of HEV-infected organs are today well documented and heparin, a porcine derived pharmaceutical isolated from porcine intestinal mucosa, has been suspected as the source of infection. We tested different commercial porcine-derived pharmaceutical products for the presence of HEV, including low molecular weight heparins, anti-rotavirus vaccines and the poractant alfa. Our preliminary results show no HEV RNA in these pharmaceutical products however given the potential risk of HEV contamination of porcine-derived pharmaceutical products further investigation is warranted to exclude these products as potential sources of HEV transmission.

Keywords: Hepatitis E virus; Porcine derived pharmaceutical products; Contamination

Body

Hepatitis E virus (HEV) has become a growing Public Health concern in the last decade in industrialized countries after the discovery of autochthonous cases of hepatitis E [1-3]. Until then, hepatitis E cases in these countries were detected only in travellers coming from HEV endemic regions of Middle East, India, Southeast Asia, Central Asia, Central and South America [4,5]. It is now known that the HEV infections acquired in high-income countries are due to zoonotic transmission, mainly due to the consumption of undercooked or raw pork meat products from infected swine [6,7]. But other routes of HEV transmission in industrialized countries have been described and others are suspected. Iatrogenic transmission such as transfusion of HEV–contaminated blood products and transplantation of HEV-infected organs are today well documented [8,9] and heparin, a porcine derived pharmaceutical isolated from porcine intestinal mucosa, has been suspected as the source of infection in a hospitalized woman that has received this anticoagulant as prophylaxis for thromboembolic disease [10]. This woman had no travel history to HEV endemiccountries, rarely ate pork products and had not received blood products during hospitalization, which lead the authors to hypothesize that the heparin the patient received might have been the source of her HEV infection [10]. Despite the efforts the authors have not detected HEV in the screened heparin batches.

But not only heparins are derived from pigs. Over 40 pharmaceuticals and medicines are derived from pig co-product [11].One of those is poractant alfa, a surfactant widely used as effective treatment for preterm infants with respiratory distress syndrome that has shown to markedly reduce pneumothorax and mortality when compared with other surfactants [12].

The manufacture processes used to prepare pharmaceuticals and medicines of animal origin must satisfy the appropriate microbiological purity criteria of the final product in order to produce therapeutically effective medicinal products and safe for the patient. However, despite these efforts, microbial contamination of pharmaceutical products has been reported of which a good example was the rotavirus vaccines contaminated with porcine circovirus [13]. Although this contamination had no serious consequences because porcine circovirus is not pathogenic to humans, this problem show that commercial biopharmaceutical porcine-derived products

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Correspondence:
JR Mesquita, Centre for Studies in Education, Technologies and Health (CI&DETS), Polytechnic Institute of Viseu, Portugal, E-mail: jmesquita@esav.ipv.pt

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could bear a risk of contamination with pathogenic human viruses such as HEV, a non-enveloped RNA virus particularly resistant to physical and chemical agents. As such, investigation is warranted to exclude these biopharmaceutical porcine-derived products as potential sources of HEV infection. The method of choice to detect traces of HEV in these matrices must be a highly sensitive method such as quantitative real-time reverse transcription polymerase chain reaction (RT-PCR). However PCR-based detection techniques are susceptible to the interference of complex matrices, such as those of some pharmaceutical products that can cause PCR inhibition. Hence, adequate controls must be used to assess the efficiency of nucleic acid extraction, reverse transcription, and PCR amplification.

In particular, heparin was identified as an inhibitor of enzymatic reactions, such as RT and PCR [14]. Although most of inhibitors of RT-PCR are removed during nucleic acids extraction, heparin presents a unique problem because it appears to co-purify with the RNA throughout numerous types of extraction procedures [14]. To overcome this problem, heparinase treatment of RNA extracts has been used to remove traces of heparin prior to quantitative real-time RT-PCR.

Our team has been interested in the problem of potential HEV contamination of porcine-derived pharmaceutical products and has devoted this topic with a task integrated in the project HEPeCONTROL, supported by European Economic Area Grants (EEA grants) 2009-2014, Public Health Initiatives' Programme (PT06), project HEPeCONTROL (60DT2) [3]. For that, we tested different commercial porcine-derived pharmaceutical products for the presence of HEV, including low molecular weight heparins, anti-rotavirus vaccines and the poractant alfa. Heparinase treatment was performed on the RNA extracts of the heparins, and quantitative RT-PCR were used with the appropriate internal controls to assess for the efficiency of nucleic acid extraction, reverse transcription, and PCR amplification. Until moment, our preliminary results show no HEV RNA in the pharmaceutical products studied.

In conclusion, given the potential risk of HEV contamination of porcine-derived pharmaceutical products investigation is warranted to exclude these products as potential sources of HEV transmission.

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