From bad to worse: the shortage of fibrinolytics

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The problem of ongoing drug shortages is increasing pressure on pharmacists, prescribers and patients. Unfortunately, this situation is nothing new. Hospital pharmacists are commonly at the forefront of this battle, investing increasing amounts of time to identify, follow-up and resolve these shortages.[1 2] While drug shortages might initially have been perceived as merely a logistical nuisance, this has now changed substantially, since patients are increasingly at risk for harm due to therapeutic agents simply not being available.

One specific shortage currently affecting healthcare systems worldwide concerns fibrinolytics, used in an array of indications. According to current estimates, global availability will not be restored until well into 2024. Reasons for unavailability include a limited number of manufacturers, (vulnerable) single-site production facilities, high(er) quality standards (along with concomitant quality issues), and last but not least an increased use of the involved drug (class).[3 4] Driving factors underlying these causes are frequently economic in nature.

Given the clinical impact of this specific shortage, a task force has been assembled by the Belgian Federal Agency for Medicines and Health Products (FAMHP). In Belgium, a clinically relevant issue has arisen with alteplase, a fibrinolytic agent primarily used to treat ischaemic stroke and haemodynamically unstable pulmonary embolism (unstable PE).[5 6] The manufacturer relies on these two indications to determine its annual forecast.

The authors of this Editorial are all active in the University Hospitals Leuven, a large, academic hospital situated in a highly urbanised region (Leuven, Belgium). Rather poignantly, our alma mater KU Leuven played a major role in the discovery, purification and later in the upscaling of tissue plasminogen activator (tPA) under the supervision of Désiré Collen, a Belgian physician, researcher and biotechnology entrepreneur. Approximately 40 years ago, this resulted in the first steps towards the use of recombinant tPA for acute myocardial infarction.[7] Unfortunately, this history, however interesting, does not provide us with any protection against the current shortage. To mitigate the effects of this shortage in our hospital, we have implemented several measures. These included calling back all alteplase vials to the hospital pharmacy department, scheduling meetings with the main prescribers to reach consensus on appropriate use (including deciding what to do in case of unavailability of alteplase), followed by explicit communication throughout the hospital. The pharmacy department applied restrictive dispensation of alteplase (ie, only for ischaemic stroke and unstable PE), and provided evaluation of and follow-up on the number of dispensed vials. Feedback was provided to prescribers at least monthly or sooner if a higher than expected use was observed. We provided feedback to the manufacturer of alteplase and consulted with the FAMHP. For ischaemic stroke, exact doses of alteplase were administered (ie, 0.9 mg/kg with a maximum dose of 90 mg; average administered dose was 70 mg), hence relying more on 20 mg vials than 50 mg vials), physicians were advised to critically review the indications and potential alternatives were pursued. Unfortunately, due to the global scale of this shortage, no (valid) alternatives were found. Strategies such as those detailed above helped to alleviate the clinical impact of this shortage but at a substantial cost in terms of time invested by all stakeholders. Luckily, no stroke or unstable PE patients were left untreated in our centre. Our measures were largely in line with those proposed by the European Stroke Organisation.[8]

Despite all efforts, Belgian healthcare professionals were unable to resolve the shortage. As a result, quotas were defined for each hospital starting in June 2022 and based on historical orders. From that point on pharmacists have had to provide weekly updates to the FAMHP. When the hospital's supplies drop below a predefined threshold (ie, 75% of the hospital's quota), an order can be placed with the manufacturer. Ad hoc urgent orders can be placed as well where the company ensures delivery within 5 hours. In January 2023, we received new information that the 2023 allocated stock for Belgium will be lowered compared with 2022. Consequently, quotas per hospital will be adapted accordingly.

The current drug shortage does not solely impact the management of ischaemic stroke and unstable PE patients as alteplase is not the only fibrinolytic experiencing a shortage. Prior to alteplase, we already experienced issues with availability of urokinase. These have not been resolved – in fact they have only become more substantial. In Belgium, urokinase is used at least as frequently as alteplase (in terms of defined daily doses), and its indications include among others the prevention of recurrent occlusion of indwelling catheters, treatment of partially and fully occluded catheters, and catheter-directed treatment of acute limb ischemia and deep vein thrombosis. Many Belgian hospitals are now using Taurolock-U (which contains taurolidine, 4% citrate and 5000 IU/mL urokinase) for the prevention of thrombosis in long-term catheters, such as in dialysis patients, and in the treatment of fully occluded catheters.[9 10] For other indications, where no alternatives are available, in our hospital we rely on on-site compounded 40 000 IU/10 mL syringes, as long as they are available.[11] While there seems to be a workable plan to ensure sufficient alteplase for stroke and unstable PE, it is becoming increasingly unclear whether this will also be the case for urokinase. Given the limited shelf life and lack of viable alternatives, we are found wanting particularly regarding the management of acute limb ischemia. Specific catheters might prove valuable, but further research is still needed to confirm their safety and efficacy.[12] In sum, while the shortage of alteplase might lead to more untreated strokes and unstable PE, both in their own right serious clinical presentations with a large impact on morbidity and mortality, the same goes for untreated acute limb ischemia.

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Furthermore, central venous access devices (eg, port-a-cath) are of paramount importance for the administration of life-saving treatments, such as anti-cancer therapies. The impact of treatment delay or cancellation because of non-functional catheters that are no longer rescuable due to a lack of fibrinolytics is difficult to measure, but substantial.

Given that each country is experiencing similar issues with these drug shortages, more support at the European level would be beneficial.[13] This might include increased collaboration between countries, sharing of information and resources, and coordinated efforts to address this issue. For example, the European Medicines Agency (EMA) has a platform for information sharing and coordination on drug shortages. Moreover, the European Association of Hospital Pharmacists (EAHP) has developed a strategy for dealing with drug shortages which includes measures such as improving communication, identifying alternatives, and promoting the use of available resources. Such initiatives highlight the importance of collaboration and coordination in addressing the current drug shortage of fibrinolytics.[14] Yet, this has not avoided the predicament we are currently facing.

In conclusion, the shortage of fibrinolytics, of both alteplase and urokinase, is a pressing issue that is affecting hospitals worldwide and will keep doing so for at least another year. The reasons for this shortage are varied and include limited competitors, single-site production facilities, and increased use. In our hospital, we have implemented several measures to mitigate the effects of this shortage, but we are not yet out of the woods. Given the new situation of even stricter quotas, Belgian hospitals have no alteplase reserves. More urgent perhaps is that the situation with urokinase remains unclear. To address the issue of this shortage of fibrinolytics, more support at the European level is needed.

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