NSW TAG NSW Therapeutic Advisory Group Inc. | Advancing quality use of medicines in NSW

Group Discussion: Meropenem and ceftazidime infusors

Date: March 2018

Question:

NSW TAG received an enquiry from a member following changes to the shelf-lives of meropenem and ceftazidime infusors.

NSW TAG and TAGNet members were asked to provide feedback regarding:

1. Current/previous use of meropenem and/or ceftazidime in HITH/OPAT; how is it administered?
2. Has the Baxter's recent reduction of shelf-life and concentration of the meropenem elastomeric devices affected your provision of meropenem infusors? What are you planning to do now?
3. Has your practice for provision of ceftazidime infusors changed given Baxter's notification of reduced shelf-life in 2017? If so, what are you doing now?

Background:

Baxter has revised the shelf-life and concentration for the meropenem infusors was the result of an audit of Baxter's UK compounding pharmacy arm. The limits of the impurities exceeded the USP assay limits, therefore the production was stopped globally.

Responses:

7 responses were received.

Liverpool Hospital

Meropenem**:** We only use meropenem that can be loaded on the day into a Sodium Chloride infusor by a trained nurse. We have done this for a long time, as our ID physicians were aware of data which indicated considerable loss of potency of meropenem in elastomeric devices and did not want to take the risks associated with that.
Ceftazadime: We don't use a lot of ceftazidime in infusors. We would probably look at changing the drug.

Concord RG Hospital

Meropenem: At Concord we have traditionally not routinely sent patients home with meropenem infusors. When there are no alternatives, we originally used 12h infusions with ice bricks but then based on a paper by Manning et al. felt it was satisfactory to use 24h infusion without ice bricks.
We had a patient who experienced ADRs to ertapenem, so meropenem was used and he has tolerated this. The Baxter shelf-life affected us, which is why I asked RNSH what they do. But on Concord's review of the data, practices done in other hospitals in Australia (SHPA ID COSP) and the patient due to finish the course soon we decided to complete this man's course with the 24h meropenem infusors. We signed a Form C from Baxter and got DTC approval.
In future, we will continue to use an alternative agent in place of meropenem. If this is unavailable, we may keep patients in hospital or look at alternative manufacturers.

Ceftazidime: We had a patient last year, and once again asked the question of other NSW hospital sites. Looking at the literature, I discussed the risks and benefits with the patient to get informed consent (which I documented in the patient record). The patient agreed and was given a course of ceftazidime infusors. We signed a Form C from Baxter and got DTC approval.
Again our patient numbers are low, as we ideally look for alternative agents.

Westmead Hospital

Westmead Hospital (adults) provided the following advice with input from the Cystic Fibrosis Service, HITH and ID.

Question 1

Meropenem and the CF service: For a number of years we've used 4.8 g Baxter infusor 240 mL over 24 hours. Baxter previously had a max shelf life of 5 days at 2-8 degrees C but no information on room temperature stability. Papers such as Manning et al (http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0102023) indicate that with meropenem at room temperature at this concentration, with degradation, patients would still receive 87% of the dose (i.e. 3.84 g from a 4.8 g infusor). Most patients receiving a 4.8 g infusor of meropenem uncooled as a continuous infusion would have meropenem concentrations above accepted breakpoints of P. aeruginosa 100% of the time.
Thus the CF clinicians felt that the CF patients were still receiving about 3.8 grams over the 24 hours, and packing the infusors with ice to maintain them at 2-8 degrees C was onerous and not warranted for our mobile patients, particularly as they were often receiving last few days of a two week course as infusors.
The meropenem infusor previously had a 5 day expiry but due to the day and time the meropenem was manufactured at Baxter and shipped to Westmead, we would usually get 4 days supply at a time, and arrange patients to come back according to that schedule.
Ceftazadime: Likewise in CF, ceftazidime up until the changes in stability information we used ceftazidime infusors of 6 g over 24 hours. This was just used by us "as is", ordered a week at a time, and not ice-packed at all. Many patients in CF are trained to manage the infusors themselves, and don't require any HITH/OPAT/PACC staff help. This works very well, and in some instances enables them to continue working or studying while on home treatment.

Question 2:

Yes it makes it very impractical to use home treatment, due to the stability constraints.
I contacted Mike Millar from Baxter who verbally responded that there weren't toxic impurities detected (such as pyridine with ceftazidime) but "impurities" refers to other degradation products of meropenem.
The maximum concentration of 6mg/mL (or 1.44 g/240 mL) is much lower than previous maximum of 20mg/mL. The concern appears to be due to enhanced degradation of meropenem and potential reduction in clinical efficacy. However, as mentioned above, other data in the literature gives a more nuanced discussion on this. A 1.44 g over 24 hour dose, needless to say, is considerably below the recommended dose of meropenem for most patients. Even with 2 infusors running it would be difficult to get adequate doses for HITH patients (unless renal impairment and on twice daily or daily dosing).

In HITH, (as opposed to CF) not much meropenem is used and ertapenem is a good option in many instances except for pseudomonal infections (and carbapenem-resistant isolates). And cefepime is an option for some pseudomonas patients, max dose of 4.8 g for an infusor, or running two infusors. Tazocin™ may still be an option pending availability and on a case-by-case basis.
There is information also about alternative providers of infusors e.g. Slade, who apparently are continuing to provide meropenem as before. This discrepancy has apparently been raised with the TGA.
At this stage, for one patient, we have signed a "Form C" with Baxter to allow us to order with the concentration and shelf life as per previous. The team has discussed the situation with the patient, who has consented and consent documented in the patient notes (as this is effectively an off-label use of the product now). This particular patient wanted to just use the infusor as she always has without ice-packing.
Data from Baxter relating to pyridine and ceftazidime, and the basis for the change in stability data is limited. We were unable to find any particular information on the toxicity of the small amounts of pyridine patients would be exposed to from the ceftazidime breakdown, nor information on cumulate exposure to pyridine from several courses of ceftazidime infusors used at room temperature over a patient's life, or what the RDI/background intake of pyridine in the diet would be anyway, or whether there are any other medications that have pyridine as a by-product and how these are dealt with. The only data we could find on pyridine was related to ingestion or inhalation of large quantities of the product (see Micromedex ToxPoints, and other toxicology texts), and an article from 1981 from the Journal of Agricultural and Food Chemistry on pyridines found in foods (indicating that the general population would be exposed to pyridines in foods anyway).
At the moment CF clinicians are avoiding discharging patients on ceftazidime infusors unless absolutely necessary although we have used the infusors as per the prior stability information, using the Form C (Director of pharmacy approval) and informed patient consent (because it was effectively using it off-label/outside the stability conditions from Baxter). A process was also used with ice packs, however there was some concern that this might affect the flow rate of the infusor.

Nepean Hospital

We very rarely use meropenem in HITH. Ceftazidime is also rare but we have a current patient at the moment. We order from MobiLife and the infusors are hooked up to patient upon discharge and then every day at the patient's house via HITH nurses travelling to their property. The MobiLife expiry date is satisfactory for us as we only order infusors week by week after each clinic review visit.

Lismore Hospital

We use very little of both so this change doesn't affect us. Meropenem expiry does not support HITH use. Since we don't use Meropenem currently, we would decide which agent to use when the time comes.

Canterbury Hospital

Currently do not use meropenem or ceftazadime infusors.

Port Macquarie Hospital

Meropenem: Not using Meropenem in infusor devices. Having to lug about freezer bricks seems a bit hard for most patients.

Ceftazidime**:** We are letting the consultant know about the by-products each time and manage the short expiry as best we can.

Other collated information regarding meropenem infusors from Australia and New Zealand cystic fibrosis pharmacists, courtesy of Westmead Hospital:

- We still use meropenem 24 hour infusors in our paediatric patients albeit occasionally.
- We haven't been using meropenem in infusers at all because of the stability problems.
- This is what we are doing: Yes, we were informed of this a few weeks ago. We are currently sending out blanks (150mL sodium chloride 0.9% infusors) and vials, so the nurses are making up. They are then being infused as previously – at fridge temp over 24hrs. It doesn't get past the maximum concentration issue, but I am aware of other hospitals seeing Baxter's data and deciding to continue as they always have anyway. I haven't seen this data, so this was a measure agreed between Home IV and ourselves.
- We teach our CF adult patients reconstitution and slow push of IV meropenem. Patients will have either PICC or PORT for IV access when on home IV therapy
- As the total daily dose of meropenem is 6g for our adult CF patients – patients who required meropenem treatment will self-administer (e.g. reconstitution and slow push via PICC or PORT) on discharge. If a patient has not self –administered antibiotics before – they are taught how to do this. All patients self – administering antibiotics will have their self-administration technique/process assessed by nursing staff during hospital stay. Also wanted to ask with regards to any centres infusing meropenem over 24 hours for Home IV– do you have any supporting data for concentrations of 6 g over 24 hours that you can share and also what temperature is the infusion running over (e.g. room temp or 'fridge' temp with ice packs etc.).
- We have patients who prefer the 24 hour bags at home for life style reasons etc. Based on Baxter letter we now have to use preloaded syringes given every 8 hours……and that may not be correct given the Baxter data states only stable for 6 hours at 25 degrees Celsius.

Responses received as at 28 March 2018