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Short communication

Evaluation of drugs for potential repurposing against COVID-19 using a tier-based scoring system

Michael A Jarvis¹,²*, Frederick A Hansen³, Kyle Rosenke³, Elaine Haddock³, Christopher Rollinson⁴, Simon Rule⁴, Graham Sewell⁵, Andrew Hughes⁶, Heinz Feldmann³

¹University of Plymouth, Plymouth, Devon, UK
²The Vaccine Group, Ltd, Plymouth, Devon, UK
³Laboratory of Virology, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Hamilton, MT, USA
⁴University Hospitals Plymouth NHS Trust, Plymouth, Devon, UK
⁵The Leicester School of Pharmacy, De Montfort University, Leicester, UK
⁶Manchester Cancer Research Centre, University of Manchester, Manchester, UK

*Corresponding author e-mail: michael.jarvis@plymouth.ac.uk

Background: As the Coronavirus Disease 2019 (COVID-19) pandemic grows daily, we remain with no prophylactic and only minimal therapeutic interventions to prevent or ameliorate severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2). Prior to SARS-CoV-2 emergence, high throughput screens utilizing clinically developed drugs identified compounds with in vitro inhibitory effect on human coronaviruses that may have potential for repurposing as treatment options for COVID-19. However, caution should be applied to repurposing of these drugs when they are taken out of context of human pharmacokinetic parameters associated with normal therapeutic use.

Methods: Our aim was to provide a tier-based scoring system to interrogate this data set and match each drug with its human pharmacokinetic criteria, such as route of administration, therapeutic plasma levels and half-life, tissue distribution, and safety.

Results: Our analysis excluded most previously identified drugs but identified members of 4 drug classes (antimalarial amino-quinolones, selective estrogen receptor modulators; SERMs, low potency tricyclic antipsychotics and tricyclic antidepressants) as potential drug candidates for COVID-19. Two of them, the tricyclic antipsychotics and tricyclic antidepressants were further excluded based on a high adverse event profile.

Conclusions: In summary, our findings using a new pharmacokinetic-based scoring system supports efficacy testing of only a minority of candidates against SARS-CoV-2 infection.

Currently, there is no licensed treatment for COVID-19 worldwide, but the FDA has recently given emergency approval for the use of Remdesivir in COVID-19 patients [1]. In addition, over 1000 clinical trials are currently ongoing or in set-up mode in different countries, including drugs such as lopinavir/ritonavir, dexamethasone, hydroxychloroquine and inhaled interferon beta-1a [2]. Overall, the current situation is far less than satisfying and there is an urgent need for additional treatment options, especially as the pandemic moves into lower resourced countries.
Over the past decade, several studies have used high throughput screens (HTS) to identify clinically developed drugs with *in vitro* inhibitory capacity against human coronaviruses (hCoVs) that may have potential for repurposing as prophylactic or therapeutic treatment options for hCoV infections. These HTS have identified >60 drugs with inhibitory effect as measured by reduction of replication of multiple hCoVs in a variety of different mammalian cell types *in vitro*. However, candidates are rarely considered in light of their pharmacokinetic parameters associated with normal therapeutic dosing. The aim of our study was to use a tier-based scoring system to interrogate this data set by matching drugs with their respective human pharmacokinetic criteria as well as their safety and systemic side effects relevant within the COVID-19 patient setting, allowing us to exclude identified HTS candidates based on these defined pharmacokinetic criteria. Remaining candidates were then further considered based on potential for adverse effects within the COVID-19 patient treatment environment.

Screening clinically approved pharmaceuticals for repurposing removes the substantial time burden associated with movement of experimental drugs from preclinical stage through the regulatory pathway to approval. Repurposing can be especially important for the rapid identification of candidate drugs against emerging infectious diseases such as the present pandemic COVID-19. With notable exceptions [3], only a few drugs have been successfully repurposed, and none for the prevention or treatment of virus infection. With this in mind, our tier-based analysis used three HTS studies as a source of clinically developed drugs with inhibitory effect against *in vitro* replication of multiple hCoVs [4-6]. Drug candidates were critically examined based on the following key pharmacokinetic parameters: route of normal administration, therapeutic plasma levels and half-life, tissue distribution, and safety and adverse reactions. Availability and cost were additional important parameters given the anticipated need for treatment options within low- and middle-income countries. These characteristics were used to i) remove candidates based on pharmacokinetic parameters and potential for adverse events not consistent with prophylactic/therapeutic use for COVID-19, and ii) prioritize remaining drugs for possible *in vitro* confirmation of SARS-CoV-2 inhibitory activity and movement into preclinical animal models (Tier 1 and Tier 2) (Table 1 and Table 2). Tier 1 represents drug candidates with administration, pharmacokinetic and safety parameters suitable for movement into preclinical models; Tier 2 represents similarly suitable candidates, but with a higher adverse event profile. Drugs in Tier 3 have a lower priority due to higher risk of complications in the COVID-19 patient setting, and Tier 4 drugs are those with low prophylactic/therapeutic potential against COVID-19 and/or with high potential for adverse effects (Supplemental Table 1).

In the study of de Wilde et al (2014) [5], a 348 FDA-approved drug library was screened for inhibitory activity against Middle East respiratory syndrome CoV (MERS-CoV), with those identified with high inhibitory effect (EC\textsubscript{50} at low micro-molar concentrations) being tested further for activity against SARS-CoV-1 and hCoV-229E. This HTS resulted in identification of 4 candidates with low micro-molar EC\textsubscript{50} concentrations against these 3 hCoVs and low cellular toxicity. The Dyall et al (2014) study [6] screened by HTS a library of 290 FDA-approved, or experimental drugs with defined molecular targets, that had previously shown activity against RNA viruses [7,8]. The study identified 27 compounds with inhibitory activity against MERS-CoV and SARS-CoV-1 with EC\textsubscript{50} levels in the low micro-molar range with minimal cytotoxicity. The 2019 HTS of Shen et al (2019) [4] screened a 2,000-component library of FDA-approved and pharmaceutically active compounds. Seven compounds
were identified with an EC$_{50}$ of <5 μM against 4 distinct hCoVs. For the purpose of our study, we expanded the inclusion criteria of Shen et al. (2019) [4] to include a total of 36 compounds with an EC$_{50}$ of <20μM for the four hCoVs and low cytotoxicity. Together, our analysis was comprised of a total of 58 compounds. We excluded 26 compounds, and identified 11 and 21 compounds with high and medium priority, respectively, with potential for therapeutic intervention against COVID-19. In addition to the single HIV protease inhibitor, lopinovir, the high priority (Tier 1 and Tier 2) compounds represented multiple members from four key drug classes: antimalarial quinolones, selective estrogen receptor modulators (SERMs), amine tricyclic antipsychotics, and amine tricyclic antidepressants.

After removal of primarily experimental agents or those with high toxicity, pharmacokinetic parameters of therapeutic plasma levels of normal dosing and plasma half-life were used as an initial measure to assess whether hCoV inhibitors reach levels required for virus inhibition within the patient. For example, loperamide, an antidiarrheal agent identified as an attractive candidate for repurposing in two HTS screens [4,5] has therapeutic plasma levels >3 orders of magnitude lower than its EC$_{50}$ against any hCoV tested [9]. This assessment resulted in removal of 26 candidates; drugs applied topically were also removed. Although multiple antipsychotics were identified by HTS as broad inhibitors of hCoV replication in vitro, only the low potency 1st generation tricyclics reached the necessary therapeutic plasma levels for inclusion (Tier 2), with the more potent later generation tricyclics commonly orders of magnitude below their EC$_{50}$.

Four distinct but structurally related members of the antimalarial quinolone class displayed inhibitory effects on multiple hCoVs. Normal therapeutic levels of these agents reached plasma levels approximating the identified EC$_{50}$ in the HTS studies. Lung tissue distribution (when available) was used as a further parameter, wherein lung tissue-specific accumulation was regarded as a positive indicator for potential therapeutic effect. Based on available data, the quinolone compounds have been shown to accumulate at high (~1000-fold) levels in the lung compared to plasma. Consistent with the prophylactic use of quinolones against malaria, most members exhibit a long plasma half-life, with oral administration being the preferred route to prevent toxicity associated with more rapid parenteral routes. Amongst the quinolones, however, amodiaquine and mefloquine were listed in Tier 2, as compared to other members, these drugs are associated with more severe and prolonged adverse reactions (Table 2). Other high priority candidates with therapeutic plasma levels approaching necessary EC$_{50}$ levels were the selective estrogen receptor modulators (SERMs) (tamoxifen and toremifene), amine tricyclic antidepressants (clomipramine and desipramine), and low potency tricyclic antipsychotics (promazine and chlorpromazine). The SERMs in particular showed high accumulation within the lung and minimal adverse reactions, and were listed in Tier 1 (Table 1). In contrast, due to a higher number of associated adverse reactions, as well as the frequent need for optimization of the dosing regimen, the antidepressants and antipsychotics were listed in Tier 2 (Table 2) [9-11].

Multiple hCoV inhibitory drugs identified by HTS with attractive pharmacokinetic profiles were prioritized lower (Tier 3) due to either their preclinical/experimental status or higher possibility for adverse reactions in the COVID-19 patient setting; otherwise attractive candidates with short half-lives were also included in this tier (Supplemental Table 1). Several antineoplastic agents were identified that interfere with DNA and RNA replication. The prodrug mycophenolate mofetil, through its mycophenolic acid active metabolite, is an inhibitor of guanosine synthesis through an inhibitory effect on
inosine monophosphate dehydrogenase; gemcitabine and hycanthone both inhibit DNA and RNA synthesis directly through distinct mechanisms. Depending on the dosage, these anti-neoplastic drugs can result in a level of immune suppression that may be contraindicated for use in COVID-19 patients, where adaptive immunity will presumably be important. Dasatinib and imatinib, small molecule inhibitors of the Abl tyrosine kinase pathway, also fell within Tier 3 for this reason. Metronomic dosing to achieve plasma levels above the EC$_{50}$, but below the immunosuppressive dose may achieve the necessary level of virus inhibition without undermining patient adaptive immune responses. Such a treatment scenario would need to be assessed in a preclinical animal model before moving to clinical studies.

Timing of therapeutic intervention against SARS-CoV-2 appears to be critical, with disease etiology changing over time: disease being a more direct effect of virus replication at early times, whilst later lung pathology being host immune response-driven. The HTS studies detailed above identify compounds based on inhibition of hCoV replication. Drug candidates are therefore expected to be more effective for COVID-19 disease management when used early. Studies using Remdesivir (GS-5734; hCoV polymerase inhibitor) highlight the altering course of disease over time and the importance of instigating antiviral measures early. Later drug administration reduced virus replication, but failed to improve lung function or disease outcome in the immunopathologic-driven stage of disease [12]. This key importance of timing may be a possible explanation for inconsistent results from recent and ongoing studies investigating repurposing of drugs such as hydroxychloroquine, which again emphasizes the need for preclinical animal challenge models before progression to human clinical trials.

To be useful clinically, drugs will need to have a minimal adverse event profile (particularly for prophylaxis); not be contraindicated in patients who have underlying medical conditions; and achieve therapeutic drug concentrations rapidly. The low potency tricyclic antipsychotics do not possess these attributes; both chlorpromazine and promazine need to be carefully titrated to optimal therapeutic doses, and many patients report a plethora of adverse events. Furthermore, they are contraindicated in patients with multiple co-morbidities which place these patients into the COVID-19 vulnerable category. The amine tricyclic anti-depressants clomipramine and desipramine face similar challenges. Half of treated patients may report somnolence and dizziness aside of other adverse events. Patients with underlying medical conditions are either more likely to experience some of these class toxicities (e.g. glaucoma, urinary retention from their anti-cholinergic properties) or be contraindicated. Furthermore, they show potential for overdose misuse and suicidal ideation as well as withdrawal symptoms even after short courses of treatment.

The protease inhibitor lopinavir, the SERMS tamoxifen and toremifene and the anti-malarials chloroquine and hydroxychloroquine have wider therapeutic indices than the tricyclic drugs and have decades of widespread clinical use across geographies, patient demographics and co-morbidities. Lopinavir’s recommended daily dose for HIV-1 infection (800mg) produces plasma levels covering the EC$_{50}$ values for pathogenic hCoVs. Tamoxifen and toremifene are customarily used at daily doses of 20mg and 60mg, respectively, for breast cancer. But higher daily doses (~600mg and 680mg, respectively) are relatively well tolerated under short durations reaching plasma concentrations after a single dose at anti-viral EC$_{50}$ levels and evidence of greater concentrations within tissue.

COVID-19 is a rapidly evolving situation. During review of the manuscript some of the drugs under consideration were tested for in vitro inhibitory activity against
SARS-CoV-2, which is shown in the accompanying tables (Table 1 & 2 and Supplemental Table 1). During this time, two pre-clinical animal studies have also reported the absence of any effect of hydroxychloroquine when used either prophylactically or therapeutically against SARS-CoV-2 replication or associated disease [13,14]. Hydroxychloroquine treatment was also recently removed from the WHO Solidarity COVID-19 clinical study based on evidence from the Solidarity trial, a Cochrane review of the drug as well as on the release of a report from the UK-based RECOVERY trial where hydroxychloroquine showed no effect on mortality rate of COVID-19 patients [15,16]. Similarly, a post-exposure prophylaxis trial showed no effect of hydroxychloroquine on the incidence of infection from high and moderate-risk exposure to SARS-CoV-2 [17]. Multiple pre-exposure prophylaxis trials remain ongoing [18]. New recent data has also shed light on a possible mechanism behind the apparent divergence in inhibitory effect of hydroxychloroquine between in vitro and in vivo studies; wherein, the virus uses a distinct entry pathway in the Vero cells standardly used for in vitro determination of drug sensitivity, compared to the pathway utilized in lung epithelium in vitro and presumably in vivo. Notably, only the entry pathway in Vero cells is susceptible to inhibition by endosomal pathway inhibitors such as hydroxychloroquine [19,20].

In summary, caution should be applied to repurposing of drugs when they are taken out of context of human pharmacokinetic parameters associated with normal therapeutic use. Our tier-based scoring system to analyze drugs identified through HTS with in vitro efficacy against one or more hCoVs resulted in the exclusion of the majority of compounds for further consideration. Similar to the quinolones, SERMs (i.e. tamoxifen and toremifene) are a class of drugs that have characteristics of low micro-molar hCoV inhibitory activity, attractive human pharmacokinetics, favorable tissue accumulation and good safety profile for use in COVID patients [9]. The next step for all potential candidates will be preclinical efficacy testing in animal models against SARS-CoV-2 challenge. Repurposing of clinically approved drugs helps remove the concern of overt drug toxicity. However, animal infection models are critical as they place the treatment within the context of the kinetics of virus infection within the host. They can also identify unexpected enhancement of disease by a drug in context of viral infection, as experienced with mycophenolate mofetil against MERS-CoV in nonhuman primates [21]. A similar enhancement effect was seen for chloroquine prophylaxis but not treatment of mosquito-transmitted chikungunya, which corresponded with an immunomodulatory effect of the drug, and again emphasizes the importance of timing in therapeutic intervention [22].

Finally, combinations of drugs are often far more effective than single compounds [23]. Therefore, these Tier 1 drugs should be considered for combined use to take advantage of possible synergy between drugs with differing modalities of virus inhibition. However, unpredicted antagonism can also result from such combinations, as was recently observed between chloroquine and Remdesivir [24]. Again, such studies initially need to be performed using in vitro cell systems and, importantly, preclinical animal models prior to considering movement into humans.

Acknowledgements
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Disclosure Statement
AH is a former employee of AstraZeneca and current shareholder of AstraZeneca who licenses tamoxifen. Other authors claim no conflict of interest.

References


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<table>
<thead>
<tr>
<th>Name of Drug</th>
<th>Plasma Levels &amp; Lung Distribution</th>
<th>Half-life</th>
<th>EC50, CC50 (µM)</th>
<th>Reason for Tier Designation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antineoplastic Drugs</strong></td>
<td></td>
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<tr>
<td>Dasatinib1 (488.0)</td>
<td>Oral administration of 100mg results in 104ng/ml (0.2µM). Accumulates (15-fold) in lung compared to plasma.1</td>
<td>&lt; 4 h 10</td>
<td>MERS(5.468); SARS(2.100) 1</td>
<td>Pros: 1) Lung levels within range of EC50; 2) Good clinical experience; Cons: 1) Short half-life 2) Potential immune suppression (potential for metronomic dosing)</td>
</tr>
<tr>
<td>Imatinib mesylate1 (589.7)</td>
<td>Following a 400mg oral dose given once daily to steady state peak plasma concentration of 1.8µg/ml (3.05µM) to 3.4µg/ml (5.76µM). Lung accumulation is not known.</td>
<td>22h 4</td>
<td>MERS(17.689); SARS(9.823) 1; SARS-CoV-2(5.32, &gt;30.86) 10</td>
<td>Pros: 1) Lung levels within range of EC50; 2) Good clinical experience; Cons: 1) Short half-life 2) Potential immune suppression (potential for metronomic dosing)</td>
</tr>
<tr>
<td>Gemcitabine HCl1 (299.7)</td>
<td>Steady-state concentration during a 10mg/m² per min infusion for 120 to 640 min is 26.9µM.</td>
<td>15 min to 1 h 4</td>
<td>MERS(1.216); SARS(4.957) 1</td>
<td>Pros: 1) Lung levels within range of EC50; 2) Good clinical experience; Cons: 1) Short half-life 2) Potential immune suppression (potential for metronomic dosing)</td>
</tr>
<tr>
<td>Hycanthone 8 (356.5)</td>
<td>Infusion of 60mg/m² results in two patients resulted in peak plasma of 1ug/ml (2.80µM) to 0.14ug/ml (0.56µM).</td>
<td>3 to 5 hours 12</td>
<td>OC43(0.16, 3.58); NL63(5.76, 3.68); MERS(11.4, 4.32); SARS-CoV-2(0.47, &gt;10) 41</td>
<td>Pros: 1) Presume lung levels within range of EC50; Cons: 1) Short half-life 2) Potential immune suppression (potential for metronomic dosing); 3) No clinical experience</td>
</tr>
<tr>
<td>Mycophenolate mofetil8 (433.5)</td>
<td>Prodrug rapidly converted to active drug MPA (see below).</td>
<td>See Below</td>
<td>OC43(1.58, 3.43); NL63(0.23, 3.01); MERS(1.54, 3.17); SARS(0.27, 3.33); SARS-CoV-2(0.47, &gt;10)</td>
<td>Pros: 1) Lung levels within range of EC50; 2) Good clinical experience 3) Suitable half-life; Cons: 1) Potential immune suppression (potential for metronomic dosing)</td>
</tr>
<tr>
<td>Mycophenolic acid (MPA)8 (320.3)</td>
<td>8ug/ml (24.97µM) to 19ug/ml (59.32µM) following a 1 to 1.75 g oral dose given twice daily to steady state in renal patients.4</td>
<td>11 to 24 h 6</td>
<td>OC43(1.95, 3.55); NL63(0.18, 3.44); MERS(1.95, 3.21); SARS(0.17, 4.18)</td>
<td>Pros: 1) Lung levels within range of EC50; 2) Good clinical experience 3) Suitable half-life; Cons: 1) Potential immune suppression (potential for metronomic dosing)</td>
</tr>
<tr>
<td>Alpenolol8 (249.3)</td>
<td>Therapeutic levels 0.025ug/ml (0.10µM) to 0.34ug/ml (0.56µM). High lung accumulation after IV administration, but only 2-fold after oral administration.13</td>
<td>2 to 7 h 3</td>
<td>OC43(1.95, &gt;20); NL63(11.88, &gt;20); MERS(10.53, &gt;20); SARS(13.97, &gt;20)</td>
<td>Pros: 1) Lung levels within range of EC50; 2) High lung accumulation and be achieved (IV administration) 3) Good clinical experience; Cons: 1) Short half-life</td>
</tr>
<tr>
<td>Propranolol8 (259.3)</td>
<td>Therapeutic level 0.02ug/ml (0.07µM) to 0.3ug/ml (1.15µM). Rabbits given a 10mg/kg subcutaneous dose had 250-fold higher levels of drug in lung than blood at 1h.14 In dogs given a 4.5mg/kg dose over 45 min, 50-fold higher levels were present in lung compared to plasma.15</td>
<td>2 to 6 h 3</td>
<td>OC43(0.48, &gt;20); NL63(8.11, &gt;20); MERS(11.01, &gt;20); SARS(13.54, &gt;20)</td>
<td>Pros: 1) Lung levels within range of EC50; 2) High lung accumulation 3) Good clinical experience; Cons: 1) Short half-life</td>
</tr>
<tr>
<td>Doxazosin mesylate8 (547.6)</td>
<td>0.01ug/ml (0.188µM) to 0.15ug/ml (0.277µM). Accumulation data not available, but prototype of family, prazosin, accumulates in lungs.16</td>
<td>20h 4</td>
<td>OC43(4.97, &gt;20); NL63(13.95, &gt;20); MERS(12.66, &gt;20); SARS(14.48, &gt;20)</td>
<td>Pros: 1) At lower limit of EC50 2) Parent, prazosin, accumulates 10-fold in lungs; Cons: 1) At lower limit of EC50</td>
</tr>
</tbody>
</table>

**Tier 3**

**Antihypertensives**

**Beta blocker**

**Alpha1 adrenergic blocker**

**Immunosuppressants**

**Guanosine synthesis inhibitors**

**DNA/ RNA synthesis inhibitors**
<table>
<thead>
<tr>
<th><strong>Antihistamines</strong></th>
<th><strong>Antiparasitics</strong></th>
<th><strong>Anticholinergic</strong></th>
<th><strong>Neurotransmitter Inhibitors</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Astemizole(^1) (458.6)</td>
<td>Conessine(^3) (356.6)</td>
<td>Chlorphenoxamine HCl(^1) (340.3)</td>
<td>Benztropine mesylate(^3) (403.5)</td>
</tr>
<tr>
<td>Papaverine(^8) (339.4)</td>
<td>Emetine(^1,8) (553.6)</td>
<td>Astemizole(^1) (458.6)</td>
<td>Lycorine(^6) (287.3)</td>
</tr>
<tr>
<td>Pros: 1) Levels at low range of EC(<em>{50}); 2) Good clinical experience Cons: 1) Levels at low range of EC(</em>{50}) 2) Short half life 3) Lung accumulation unknown</td>
<td>Pros: 1) Experimental 2) Moderate to low accumulation in lungs Cons: 1) Lung levels below range of EC(_{50}) (may be overcome by lung accumulation) 2) Induces emesis in patients</td>
<td>Pros: 1) Levels within range of EC(_{50}) 2) High lung accumulation 3) Good clinical experience Cons: 1) Short half-life 2) Withdrawn due to rare fatal arrhythmias</td>
<td>Pros: 1) Levels far below EC(_{50}) 2) short half-life 3) assume poor lung accumulation based on diphenhydramine</td>
</tr>
</tbody>
</table>
**Calcium channel blocker**

<table>
<thead>
<tr>
<th>Drug</th>
<th>PK Data</th>
<th>Cons</th>
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<tbody>
<tr>
<td>Tetrandrine&lt;sup&gt;8&lt;/sup&gt; (622.8)</td>
<td>Oral administration of 100mg results in 67ng/ml (0.05uM) peak plasma concentration. Berbamine is a key metabolite, with same study showing 33ng/ml (0.056uM).&lt;sup&gt;28&lt;/sup&gt; Concentrated 8-fold in lungs compared to plasma.&lt;sup&gt;29&lt;/sup&gt;</td>
<td>24hr&lt;sup&gt;28&lt;/sup&gt; OC43(2.9, &gt;20); NL63(2.05, &gt;20); MERS(12.68, &gt;20); AS9(4.81, &gt;20)&lt;sup&gt;29&lt;/sup&gt; Cons: 1) Experimental in US. Approved in China for treatment of silicosis.</td>
</tr>
</tbody>
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**Interferon inducer**

<table>
<thead>
<tr>
<th>Drug</th>
<th>PK Data</th>
<th>Cons</th>
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</thead>
<tbody>
<tr>
<td>Tilorone&lt;sup&gt;8&lt;/sup&gt; (483.5)</td>
<td>At a well tolerated 10mg/kg dose, peak plasma concentration is 135ng/ml (0.28uM) in males and 92.3ng/ml (0.19uM) in females. At 2mg/kg, 50.5ng/ml (0.10uM) and 17.5ng/ml (0.036uM), males and females, respectively.&lt;sup&gt;30&lt;/sup&gt; In mice 20-fold higher accumulation in lung than serum.&lt;sup&gt;21&lt;/sup&gt;</td>
<td>20 h&lt;sup&gt;26&lt;/sup&gt; OC43(0.32, &gt;20); NL63(6.89, &gt;20); MERS(10.56, &gt;20); AS9(16.11, &gt;20)&lt;sup&gt;5&lt;/sup&gt; Cons: 1) Experimental in US. Marked as Amixin, Lavomax as an antiviral in Russia.</td>
</tr>
</tbody>
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**Antiplatelet**

<table>
<thead>
<tr>
<th>Drug</th>
<th>PK Data</th>
<th>Cons</th>
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<tbody>
<tr>
<td>Ticlopidine&lt;sup&gt;8&lt;/sup&gt; (263.8)</td>
<td>For reduction of risk nonfatal stroke normal dose is 250mg twice daily. Oral administration of 250mg results in peak plasma concentration of 0.08ug/ml (0.30uM) to 0.8ug/ml (3.03uM). Lung distribution not known.</td>
<td>20 to 50 h&lt;sup&gt;32&lt;/sup&gt; OC43(1.41, &gt;20); NL63(15.65, &gt;20); MERS(11.25, &gt;20); AS9(14.28, &gt;20)&lt;sup&gt;5&lt;/sup&gt; Pros: Within range of EC&lt;sub&gt;50&lt;/sub&gt; 2) Good clinical experience 3) Long half-life Cons: 1) Lung accumulation unknown 2) Intensive patient management.</td>
</tr>
</tbody>
</table>

**Low potency tricyclic antipsychotics**

<table>
<thead>
<tr>
<th>Drug</th>
<th>PK Data</th>
<th>Cons</th>
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<tbody>
<tr>
<td>Triflupromazine HCl&lt;sup&gt;1&lt;/sup&gt; (388.9)</td>
<td>No PK data. Assume comparable to chlorpromazine of this class.</td>
<td>23 to 37 h&lt;sup&gt;4&lt;/sup&gt; MERS(5.758); SARS(6.398)&lt;sup&gt;1&lt;/sup&gt; Pros: 1) Comparable to Tier 1 low potency antipsychotics Cons: 1) Discontinued in US.</td>
</tr>
</tbody>
</table>

**Tier 4**

<table>
<thead>
<tr>
<th>Drug</th>
<th>PK Data</th>
<th>Cons</th>
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</thead>
<tbody>
<tr>
<td>Anisomycin&lt;sup&gt;1&lt;/sup&gt; (265.3)</td>
<td>NR* NR</td>
<td>MERS(0.003); SARS(0.191)&lt;sup&gt;1&lt;/sup&gt; Cons: 1) Experimental 2) High toxicity</td>
</tr>
<tr>
<td>Salinomycin sodium&lt;sup&gt;8&lt;/sup&gt; (773.0)</td>
<td>NR NR</td>
<td>OC43(0.29, 1.97); NL63(5.71, 2.41); MERS(5.49, 3.84); AS9(5.16, 2.45)&lt;sup&gt;8&lt;/sup&gt; Cons: 1) High toxicity 2) Not used in humans. Animal feed additive.</td>
</tr>
<tr>
<td>Valinomycin&lt;sup&gt;8&lt;/sup&gt; (1,111.3)</td>
<td>NR NR</td>
<td>OC43(4.43, 6.15); NL63(1.89, 4.12); MERS(6.07, 5.88); AS9(6.78, 5.11)&lt;sup&gt;8&lt;/sup&gt; Cons: 1) High toxicity</td>
</tr>
<tr>
<td>Dihydrocelastryl diacetate&lt;sup&gt;8&lt;/sup&gt; (536.7)</td>
<td>NR NR</td>
<td>OC43(1.17, &gt;20); NL63(0.65, &gt;20); MERS(10.58, &gt;20); AS9(4.24, &gt;20)&lt;sup&gt;8&lt;/sup&gt; Cons: 1) Experimental use</td>
</tr>
<tr>
<td>Cetylpyridinium chloride&lt;sup&gt;8&lt;/sup&gt; (340.0)</td>
<td>NR NR</td>
<td>OC43(4.31, 8.23); NL63(1.24, 8.52); MERS(0.69, 8.14); AS9(7.86, 8.19)&lt;sup&gt;8&lt;/sup&gt; Cons: 1) Cationic disinfectant 2) Ingredient of mouthwash and poorly absorbed 3) No systemic PK data</td>
</tr>
<tr>
<td>Monensin sodium&lt;sup&gt;8&lt;/sup&gt; (692.9)</td>
<td>NR NR</td>
<td>OC43(3.81, &gt;20); NL63(1.54, &gt;20); MERS(3.27, &gt;20); AS9(0.18, &gt;20)&lt;sup&gt;8&lt;/sup&gt; Cons: 1) High toxicity 2) Not used in humans.</td>
</tr>
<tr>
<td>Oligomycin&lt;sup&gt;8&lt;/sup&gt; (791.1)</td>
<td>NR NR</td>
<td>OC43(0.19, 6.56); NL63(2.63, 4.26); MERS(0.21, 5.16); AS9(6.43, 6.78)&lt;sup&gt;8&lt;/sup&gt; Cons: 1) High toxicity</td>
</tr>
<tr>
<td>Cycloheximide&lt;sup&gt;1,8&lt;/sup&gt; (281.4)</td>
<td>NR NR</td>
<td>OC43(0.43, 3.12); NL63(2.64, 3.24); MERS(2.56, 2.96); AS9(5.21, 3.19)&lt;sup&gt;8&lt;/sup&gt; MERS(0.189); SARS(0.043); SARS-CoV-2(0.58)&lt;sup&gt;44&lt;/sup&gt; Cons: 1) High toxicity</td>
</tr>
<tr>
<td>Exalamide&lt;sup&gt;8&lt;/sup&gt; (221.3)</td>
<td>NR NR</td>
<td>OC43(1.48, &gt;20); NL63(17.49, &gt;20); MERS(15.91, &gt;20); AS9(16.39, &gt;20)&lt;sup&gt;8&lt;/sup&gt; Topical application (anti-fungal). Not used systemically.</td>
</tr>
<tr>
<td>Category</td>
<td>Drug</td>
<td>Route</td>
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<tr>
<td>-------------------------------</td>
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</tr>
<tr>
<td>Antihypertensives</td>
<td>Berberine</td>
<td>Oral</td>
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<td></td>
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<tr>
<td></td>
<td>4’-Hydroxysalchalone</td>
<td>Experimental</td>
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</tr>
<tr>
<td>Other</td>
<td>Loperamide</td>
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<tr>
<td>Category</td>
<td>Compound</td>
<td>Description</td>
</tr>
<tr>
<td>-------------------</td>
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<td>------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Urinary analgesic</td>
<td>Phenazopyridine</td>
<td>Following standard 200mg oral dose, peak plasma levels of 0.012ug/ml (0.056uM). No substantial accumulation in the lung (maximum 1.8-fold at 2 h post 100mg/kg dose in rats).</td>
</tr>
<tr>
<td>Quinoid-type triterpene</td>
<td>Pristimerin</td>
<td>Following oral dose of 2mg/kg in rats, peak plasma level 0.19ug/ml (0.41uM). Tissue distribution is not known.</td>
</tr>
<tr>
<td>Musc relaxant</td>
<td>Zoxazolamine</td>
<td>Single oral dose of 0.75 to 1g results in peak plasma levels of 3ug/ml (17.8uM) to 12ug/ml (71.2uM). Lung accumulation not known, but no accumulation in other multiple tissues (muscle, kidney, liver, brain or fat) in dogs.</td>
</tr>
</tbody>
</table>

NR: Not relevant
References (Supplemental Table)


24. Pendopharm DoP, Inc. Montreal, Quebec, Canada. Prescribing Information Bentropine Mesylate Tablets, USP 1mg BM Oral Solution 0.4mg/ml. 2015


